Cannabis Crashes

Myths & Truths

BY

SCOTT MACDONALD

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Preface

Over the past century, alcohol intoxication has been identified as the most important contributor to traffic fatalities and is strongly related to all types of automobile crashes (i.e. less harmful collisions). Thousands of studies showing consistent findings of ***performance deficits*** from alcohol form a strong evidence base for these conclusions. The advent of the quick and portable Breathalyzer test for alcohol ***impairment*** paved the way for effective interventions to reduce casualties from drinking and driving. Widespread deterrence-based legislation has demonstrated the effectiveness of prohibiting driving at various cut-off levels of ***Blood Alcohol Content (BAC),*** expressed as a percentage of alcohol in the blood. Scientists and most citizens accept these facts.

The story is considerably different with respect to cannabis. In this book, I will describe why knowledge about alcohol cannot be directly applied to cannabis. There is research on cannabis and performance deficits, as well as drug tests to detect cannabis use; however, many findings are dissimilar to those for alcohol, and the quality of the research is considerably worse. In many instances, authors from these scientific studies draw conclusions that are not justifiable from the methods used. Some of these faulty conclusions have become widespread beliefs in society, generating myths about cannabis use.

In Western societies of the 20th century, total prohibition of cannabis use and sales has been the predominant approach. More recently, however, numerous U.S. states and countries such as Canada have legalized recreational use of cannabis. In preparation for legalization, the Government of Canada (2017a) readied a backgrounder report that describes proposed legislative changes for laws in relation to cannabis and driving.

Canadian legislation permits roadside oral fluid (saliva) tests when law enforcement officers reasonably suspect drivers are under the influence of cannabis. Following a positive reading, officers could demand a drug evaluation in the form of a blood sample. A blood test reading of 2 to 5 ng/mL ***Tetrahydrocannabinol (THC)*** in ***whole blood*** would be subject to a summary (i.e. less serious) criminal conviction and a reading over 5 ng/mL could be

subject to an indictable (i.e. more serious) offence. Those with both a BAC of over .05% alcohol and over 2.5 ng/mL THC could be charged with an ***indictable offence***.

These legislative recommendations may be challenged under the Canadian Charter of Rights. The major question addressed in this book is **how to set cut-off thresholds for cannabis drug tests.** The first step in this process is to evaluate the ***validity*** of different cut-offs using an epidemiological approach. Societal values and legal guidelines can then be used to recommend legislation with an understanding of the validity of different drug tests. The aim of this book is to provide readers with objective scientific information about cannabis performance deficits and how to measure them.

A primary focus in this book is the validity of drug tests based on cut-off levels of ***compounds*** in biological fluids (i.e. blood, oral fluids and urine) in assessing performance deficits that could be considered impairment. In order to draw conclusions, the quality and cut-off values found in research related to alcohol risk assessment are compared to those associated with cannabis. I have summarized key issues that emerged from my research. For those who do not have a background in social science research, it may be worthwhile to review the ***glossary of terms*** to better understand some of the scientific concepts presented here. Any term the reader encounters in ***bold and italics*** can be found there.

Much of the material and my interpretation of studies presented in this book are derived from my career as a scientist and professor. I have published over 100 peer-reviewed papers, specializing in substance use and injuries, and have been an expert witness in over 20 court hearings involving drug testing in the workplace. During this process, the papers I have read ranged greatly in quality.

I have witnessed the science behind our understanding of cannabis and traffic crashes evolve greatly over the past two decades. Initially, authors of a 1999 review concluded that: “There is no evidence that consumption of cannabis alone increases the risk of culpability for traffic crash fatalities or injuries for which hospitalization occurs, and may reduce those risks” (Bates & Blakely, 1999; p. 231). A few years later a conclusion drawn from a major ***meta-analysis*** was: “Acute cannabis consumption is associated with an increased risk of a motor vehicle crash…” (Asbridge et al., 2012; p. 1). These disparate interpretations reflect the progression of our knowledge; both interpretations were well-founded, given the quality of the scientific studies at the time. However, many other conclusions have been drawn since 1999 that, in my opinion, are not justified by the

scientific methods used. In this book, I identify some of the issues that have created myths in the study of cannabis and vehicle crashes.

This book is intended for several audiences, including students, policymakers, lawyers and experts in the field of substance use and crashes. I review in detail some methodological and statistical issues of studies, relying principally on the discipline of epidemiology and biostatistics. The focus is on and the degree to which conclusions from studies are justifiable by the methods used. As well, I review relevant studies on cannabis and crashes and the validity of biological drug tests to identify those who are impaired.

CHAPTER 1

Introduction

CANNABIS LEGISLATION

In 2018, Canada became the second country in the world to legalize cannabis, after Uruguay legalized it in 2013. As of 2020, a total of 13 U.S. states also permitted the sale of cannabis for recreational use, although federal regulations still made cannabis illegal. Legalization is a response to widespread acceptance of the drug and normalization of its use. In 2002, the Canadian Senate Special Committee on Illegal Drugs Laws indicated that laws are a source for normative rules that should be used sparingly while respecting the freedoms of individuals to seek their own well-being (Nolin and Kenny, 2002). As well, they noted that criminalization is costly to enforce and largely ineffective in deterring use. The origins of cannabis criminalization date back to 1923 in Canada, galvanized by a movement spearheaded by Emily Murphy, a police magistrate, who described cannabis users as raving maniacs, liable to kill or indulge on any form of violence to others (Hathaway and Erickson, 2003, p. 467). Impartial research on cannabis has been limited and many studies have major scientific flaws. As a consequence, many myths and unknowns about cannabis existed under criminalization, which impede sound policy.

Other less drastic options than legalization were available, such as decriminalization, where possession is not subject to criminal convictions but those caught could still be subject to penalties, such as fines. Many countries have decriminalized cannabis, including Portugal, Switzerland, Italy, Mexico, Russia and Norway. Decriminalization is sometimes considered a halfway measure because a substance's use is not condoned, but tolerated.

The Canadian government's decision to legalize has been met with opposing viewpoints. Those against legalization have argued it will provide greater access to minors by normalizing pot and say that more road deaths will occur due to cannabis-impaired drivers. Those for legalization see it as an end to an overly invasive intrusion of a human's right to choose their own destiny.

Legalization involves a political trade-off. A tougher stance on some cannabis harms, such as impaired driving, may appease detractors and not overly alienate voters who staunchly support legalization. Opinions of voters may have more influence on legislation than empirical evidence of minimizing harms. Yet science can be useful to provide a good basis for the rationalization of different types of laws. The Canadian government has passed legislation to address cannabis-impaired driving, described in more detail in Chapter 2. The laws proposed include measures to detect impaired driving at low blood THC thresholds similar to many other countries worldwide. In this book, I focus on the empirical studies on the relationship between cannabis and ***impairment***[1] with the aim to better understand what ***per se*** laws aimed at minimizing cannabis-impaired driving are likely to achieve.

TRAFFIC CRASHES DUE TO ALCOHOL AND CANNABIS

Many people feel that our experiences with alcohol and crashes can help inform legislative approaches for cannabis. Impairment by alcohol while driving is a major contributor to traffic crashes. Recent figures from the U.S. show alcohol-impaired fatalities accounted for 31% of all traffic fatalities in 2014. In Canada, 22% (about 400) of fatally injured drivers were impaired above a .08% BAC in 2012, and 33% had a positive reading for alcohol use (International Transport Forum, 2016). A roadside survey of drivers in British Columbia, Canada, found 7.8% had been drinking, compared to 32% found with positive BAC in fatal crashes (Beirness and Beasley, 2010). Such data, along with several high-quality ***case-control*** studies, point to alcohol as a major risk factor for traffic fatalities and collisions.

[1] See the section "PERFORMANCE, IMPAIRMENT AND SAFETY" in this Chapter for a more detailed description of impairment.

The quality of data for cannabis and traffic crashes/fatalities is significantly weaker than for alcohol. Researchers agree that driving while intoxicated by cannabis increases the risk of car accidents; however, the magnitude of this risk varies, depending on the geographic location of the study, type of crash (i.e. fatality, injury, or property damage), biological cut-off level, and data collection methods. By all accounts, the average risk is low compared with alcohol. A recent study estimated that cannabis-attributable crashes have caused about 75 deaths in Canada (Wettlaufer et al., 2017), much lower than the number of traffic fatalities caused by alcohol. Again, the quality of the data for cannabis-related crashes is poor, and this study likely overestimated the number of deaths by using a low THC cut-off of 5 ng/mL in oral fluids, which corresponds to roughly .2 ng/mL THC in blood. As demonstrated in this book, crashes are not likely to be attributed to cannabis use near this cut-off.

In the U.S., for the period between 1993 and 2010, 29.3% of drivers in fatal crashes were tested for drugs (Wilson et al., 2014). Among those tested, 11.4% of drivers were positive for any drug, and cannabis-positive cases accounted for about one-third of those cases (Wilson et al., 2014). In Canada, the percentage of drivers involved in a fatal collision tested for drugs is higher at 77.4%, with about 40% testing positive for a substance other than alcohol, but tests specifically for cannabis were not reported (International Transport Forum, 2016). Another Canadian study of blood tests among fatally injured drivers over a 10-year period found 13.9% tested positive for drug use but again, specific figures for cannabis have not been reported (Beirness et al., 2013).

Existing data sets and research have several limitations. A comparison group of drivers not involved in crashes is not available and if control subjects exist, methods for data collection differ from those in crashes introducing ***selection biases***. Therefore, accurate risks cannot be estimated. Universal testing with disaggregated data for each drug and detailed concentration levels are often unavailable. Our understanding of the relationship between drug concentration levels in the blood and impairment or accident risk remains poor.

Aside from major differences in the quality of the research, the issue of defining impairment is central to both cannabis and alcohol. In Canada and the U.S., impairment from alcohol has a legal definition, typically defined as BAC cut-off of .05% or .08% alcohol with legislation that prohibits driving at these levels. Studies show that practically all people at these levels have reduced skills needed for driving (Fell and Voas, 2014). If a ***diagnostic***

test, such as drug test results, are used to classify people as representing a safety risk, then a threshold for defining impairment should be established. Experimental ***laboratory studies*** have found performance deficits at lower BAC levels, but the extent to which drivers at these lower levels could be causally implicated in crashes is largely unproven. In this book, alcohol impairment refers to thresholds of at least .05% alcohol concentration. Performance deficits are defined more broadly to include any decrements in psychomotor, perceptual, or cognitive functioning. In this book, I aim to find equivalent impairment thresholds for cannabis as those for alcohol in terms of traffic-safety risks.

Trends in alcohol and cannabis use driving

In a paper I published almost two decades ago (Macdonald, 2003), I examined trends in alcohol-related crashes, and noted that most industrial countries experienced reductions in these crashes over the past few decades. During this same period, the population became much older, with more female drivers, and I wondered the extent to which the overall declines were due to these changing protective demographics. These trends in demographic populations accounted for about 18% of the total decline and the remainder of the reduction was due to real changes in driver behaviour at a population level. A recent report, (Robertson et al., 2018) showed continued declines since 1986 in impaired driving, yet alcohol-related fatalities comprise a substantial proportion of all traffic fatalities.

By contrast, trends for cannabis-related driving and crashes are largely unknown. Legalization has been viewed by some as a major concern in relation to greater cannabis-related driving since legislative barriers will permit more people to use cannabis. Certainly, our experience since prohibition of alcohol has shown large increases in drinkers. However, the recent decades of decline in alcohol-related driving have occurred while the proportion of drinkers has remained fairly stable. Thus, it seems possible that populations can learn to separate use of cannabis from harmful use. In other words, use can be restricted to safer settings. Much still needs to be learned about cannabis legalization and driving.

The ***prevalence of use*** of alcohol and other drugs can be estimated from surveys, (Canadian Alcohol and Drug Use Monitoring Surveys (CADUMS) from 2004 to 2011; Health Canada, 2015). These data show slight declining trends in use for cannabis and alcohol in Canada from 2004 to 2011. In 2011, the population with past-year use was estimated at

78% for alcohol and 9.1% for cannabis. Prevalence of past-year cannabis use appears to be increasing moderately with 12% reporting any use in 2013, while alcohol use was largely unchanged from 2013, at 77% prevalence in 2015.

A question of importance is how frequently does the population engage in driving while under the influence of alcohol or cannabis? About 1.9% of surveyed adults in Ontario, Canada reported they drove within one hour after smoking cannabis (Walsh & Mann, 1999). By contrast, Beirness and Davis (2007) reported 11.6% of Canadians admitted to driving within an hour of having two or more drinks. More recently, Statistics Canada reported that 14% of cannabis users with a driver's license said they drove within two hours of consumption (Statistics Canada, 2018).This question also has been addressed by random roadside studies of drivers. Beirness and Beasley (2010) conducted a random roadside study where 78% of drivers stopped consented to a Breathalyzer test for alcohol and an oral fluid test for cannabis. About 8.1% had a positive alcohol test and 4.6% had a positive cannabis test. In a study with blood tests among fatally injured drivers in Ontario, Canada, 12.5% of drivers tested positive for cannabis and 11.1% were positive for alcohol (Beirness et al., 2020). Given that oral fluid and blood tests for cannabis have a much longer detection window (possibly days) than for alcohol, the comparison between the two is not equal. The Breathalyzer detects the acute use of alcohol whereas other drug tests detect drug use in general, which may or may not include the acute effects. Compared to cannabis, alcohol contributes a much greater burden in terms of the number of injuries and deaths due to crashes. Some believe that the reason for this fact is that most people drink and only a minority use cannabis. Although more people drink than use cannabis, as shown in this book, the ***absolute harms*** from alcohol are greater than those from cannabis.

The history of alcohol and cannabis legislation

Both alcohol and cannabis are similar in terms of governmental interventions to control their use. Historically, alcohol was prohibited in the provinces of Canada during World War One and repealed in the 1920s, with Prince Edward Island the last to abolish in 1948 (Hallowell, 2015). Today, several Canadian communities, primarily indigenous reserves, forbid alcohol use and sales. In the U.S. prohibition existed from 1919 to 1933. During periods of prohibition, there was a polarization of attitudes toward alcohol until the scales finally tipped in favour of repeal (Tyrell, 1997). This polarization appears to be related to the emergence of various myths about alcohol in terms of its benefits and harms. One

myth that emerged during prohibition was regarding alcohol's medicinal benefits. During that period, alcohol could be obtained legally with a doctor's prescription. Prescriptions were possible for a wide range of ailments, such as cancer, indigestion and depression (Okrent, 2010). Today, prescriptions like these for alcohol are rare. In terms of harms, prohibitionists also promoted some outrageous claims. For example, claims were levelled that alcohol was distilled from noxious ingredients including hemlock, opium and excrement, or that drinkers could spontaneously combust (Kelly, 2014). Since prohibition, polarized opinions still exist; however, alcohol regulations have become less stringent as alcohol is socially accepted.

Today, cannabis in Canada and in several U.S. states is in a period of transition from prohibition to legalization, replete with polarized views and murky claims. On the anti-prohibition side, we have seen the emergence of medical cannabis for a wide variety of ailments, similar to what occurred during the prohibition of alcohol. Although some medical uses have been scientifically proven, others have not (Committee on the Health Effects of Marijuana, 2017; Watson et al., 2013). Opposing these views, prohibitionists have linked cannabis use with immigration, poor school performance, and claims that users would become maniacs liable for violence (Broughton, 2014). Legislation aims to balance these opposing societal views.

The Canadian government has recommended ***per se*** laws against driving under the influence of cannabis that are not dissimilar to many other countries. In this book, I review these laws by drawing comparisons to laws against drinking and driving. I look at performance deficits with the use of alcohol and cannabis, and assess the utility of different interventions for detecting their use among drivers and workers. I also review the different methods of detecting alcohol and drug use through biological tests. A major focus of this review is the validity of the different tests to detect impairment given evidence of performance deficits. I examine the research evidence for detecting alcohol impairment and compare the approaches and findings to cannabis. As will be seen, the differences are substantial. At the end of the book, I speculate on the reasons and repercussions for these different standards.

Disciplinary focus

In this book, I assess research from an epidemiological and bio-statistical perspective on the validity of diagnostic tests for cannabis impairment, and studies on cannabis, performance and crashes. Epidemiology and biostatistics is a discipline aimed at understanding the causes of diseases and intervention approaches. A major concern with epidemiology is the minimization of ***biases*** in research designs which can distort findings. Biostatistics involves objective analyses of data. The discipline of epidemiology and biostatistics is ideally suited for the study of the relationship between road crashes and cannabis. In this context, epidemiology is suitable for assessing the validity of biological tests to detect impairment or performance deficits (Gordis, 2014). Also, epidemiology methods prescribe optimal procedures for unbiased research designs, including laboratory studies and ***observational studies*** (Gordis, 2014). Finally, biostatistics aims to provide an objective analysis of data collected in studies. These approaches are both descriptive (measures of ***central tendency*** and ***dispersion*** of a variable) and analytic to determine the strength and direction of relationships among one or more variables. I focus on issues that are particularly relevant to the issue of the relationship between crashes and cannabis use, and the measurement with biological tests of impairment associated with increased crash risk. Since research on substance use and crashes is multi-disciplinary, some limitations of studies may originate from research disciplines that do not emphasize the issues of importance in epidemiology and biostatistics. An overarching principle of research is ***transparency*** - open and clear communication of methods.

PERFORMANCE, IMPAIRMENT AND SAFETY

The focus of this book is performance deficits related to alcohol or cannabis use, and how these deficits increase the risk of traffic crashes. I draw a distinction between impairment and performance deficits.

- ***Performance deficits*** refer to the degree to which deficits occur under different conditions, which may or may not translate into dangerous driving.
- ***Impairment*** refers to a specific threshold at which driving a vehicle due to performance deficits is dangerous for nearly all people. For alcohol, this threshold is a BAC of .05% or greater.

Understanding the distinction is important for interpreting the research. The term impairment has two meanings: one of common usage and one of a threshold where people can be classified as either a safety risk or not. In common usage, the term impaired is sometimes used to indicate any performance deficits. In a more technical and legal sense, impairment refers to a threshold which performance is unsafe. In this book, I sometimes refer to impairment to indicate performance deficits because this is how others have described it. Mostly, however, I use the term to imply a threshold where subjects with this condition can be considered a meaningful safety risk.

Impairment from a legal perspective implies some level of performance deficits that practically all people would experience; these deficits would also significantly increase crash risk. This definition applies to alcohol impairment, described by Fell and Voas (2014). Impairment is a threshold of performance deficits that can be used to distinguish groups as either posing a safety risk or not. One reason for drawing this distinction between performance deficits and impairment is because impairment is typically a legal definition that refers to a specific alcohol concentration that constitutes a legal offence. Performance deficits may also occur at lower levels of consumption, but are not at a sufficient magnitude or meaningfully related to crash risk to constitute impairment. Reference to any performance deficit as impairment obscures the difference between the two. This distinction has not always been made by researchers. For example, Moskowitz and Florentino (2000) define any performance deficit as impairment. In this book, a distinction is made between performance deficits and impairment. For impairment, a threshold is used to classify individuals into one of two groups: either impaired or not impaired. On the other hand, performance deficits can be treated as a ***continuous variable,*** with deficits ranging from mild to severe and may include impairment.

An important distinction of deficits is the difference between an absolute standard versus a relative one. A person's skill and performance in operating a vehicle varies considerably from one person to the next, and performance for any individual can vary based on a number of factors at different times. Some people are more competent drivers than others. It stands to reason that when drivers experience different types of performance decrements, their ability to drive will be affected in different ways. Excellent drivers may become only good drivers, whereas average drivers may become poor when experiencing deficits. As well, a great deal of variation exists in terms of how drivers cope with these deficits in that some may successfully compensate whereas others may not.

What this means in real terms is that some drivers may still be capable of driving while experiencing various risk factors for crashes. Absolute standards refer to definite criteria needed to drive a car, such as understanding the rules of the road and being able to manoeuvre a vehicle satisfactorily.

Any threshold of impairment should be based on a trade-off between the proportion of false positives and false negatives and the consequences for each, which can vary depending on contexts. Safety issues must be weighed based on the validity of the tests, the magnitude of penalties for false positives and the safety consequences of false negatives. Assuming that the drug concentration levels bear some relationship to impairment, lower thresholds will increase false positives (reduce specificity) and decrease false negatives (increased sensitivity). Whether a particular cut-off is justifiable depends on these trade-offs.

Other risk factors for crashes

Numerous risk factors that increase crash risk have been found in research, such as traits including aggressiveness, impulsivity, disrespect for authority and depression (Macdonald, 1989). Stressful life events, such as the death of a family member or marital separation, also are related to an increased likelihood of serious traffic crashes (Lagarde et al., 2004; Lehman et al., 1987). Fatigue is also known as a risk factor for traffic crashes (Dawson & Reid, 1997). Both younger and older driver are at elevated risk of crashes (Eustace and Wei, 2010).

Although risk factors can be identified with empirical research, the identification of deterrence-style interventions to prohibit drivers for many situations currently are not feasible. Only educational approaches are feasible. A comparison to the magnitude of numerous factors for safety risk pose challenges for defining substance impairment. A fair biological threshold should be valid enough to correctly classify individuals into meaningful groups.

A major risk factor for crashes is distracted driving. In order to drive safely, drivers must be continuously focused on driving. Other activities, such as driving while smoking cigarettes (Sacks & Nelson, 1994) or eating and drinking while driving (Lombardi, 2003) are distractions from the task of driving and increase the risk of crashes. There is good evidence that cell phone use greatly increases crash risk. Although cell phone use while driving has been identified as a risk factor for crashes and an offence in most jurisdictions, many other

potential safety risks are ignored and to some extent encouraged. For example, cup holders and ash trays in cars encourage distractions by drinking coffee or smoking cigarettes. Although ashtrays are not common today based on manufacturers choices, cup holders are very prevalent. No laws exist to ban drinking non-alcoholic drinks or smoking cigarettes, yet they both can be distractions from driving. Drive-through restaurants on highways also appear to encourage distractions of eating while driving. A simple study could examine crash rates before and after drive-through restaurants on highways. Legislators could easily ban ashtrays and cup holders for drivers, yet both can be installed in cars. The priority is safety and non-invasive simple interventions that promote safety should be our major priority.

Some activities are clearly more popular than others but safety should not be based on their effectiveness. Laws based on popularity rather than science have the potential to be discriminatory. Discrimination is drawing judgements about individuals based on perceived or actual characteristics of groups. Some might regard cannabis users as careless, irresponsible, to have little regard for the law, and to frequently drive after using cannabis; however, in this book, driving after cannabis use is examined as a safety issue. Unfortunately, some safety issues do not have simple legislative solutions. Solutions that penalize those who use cannabis rather than those who use cannabis in an unsafe manner, such as while driving, are discriminatory. The best laws are those that focus on changing the driving environment and provide measurable safety benefits.

RESEARCH QUESTIONS

In this book, I address three overarching questions:

1. What is the validity of biological tests for alcohol and cannabis to impairment?
2. What is the relationship between cannabis use and performance deficits?
3. How effective are alcohol and cannabis per se laws at improving traffic safety?

Several pertinent sub-issues exist to address these major questions are described in each Chapter of this book. In Chapter 2, legislative approaches for impaired driving and the validity of studies that use biological drug tests to detect impairment by cannabis are described. A closely related issue is the strengths and limitations of biological drug tests (Chapter 3). An important issue with respect to understanding the value of drug tests is

related to movement of alcohol and cannabis in the human body or pharmacokinetics (Chapter 4). Next in Chapters 5, the acute effects of alcohol and cannabis are described, whereas in Chapter 6 research on the non-acute (i.e. withdrawal effects, hangover effects, and long-term cognitive deficits) effects of alcohol and cannabis is reviewed. Then in Chapter 7, studies that involves actual crashes and determinations of risk from alcohol and cannabis are described. The final Chapter 8 provides an overall assessment of what was learned in this book.

Epidemiological principles for conducting research related to these topics are included. These principles have been developed and articulated to provide a guide on how research should be conducted to ensure objective conclusions are drawn. Unfortunately, many research studies have major limitations, often unacknowledged by the authors. In good research, limitations of studies should be noted by authors so that readers can properly assess the meaning of research findings. Nevertheless, major limitations are not always highlighted by researchers, either because the authors are unaware of the limitations, or they are aware but wish to present their findings in a positive manner. I will identify the flaws in some studies and demonstrate why the conclusions by authors are not justified by the methods used.

CONCLUSION

In this Chapter, an overview is given on parallels and differences between alcohol and cannabis in terms of traffic-safety risks and potential intervention approaches. In order to assess the magnitude of these safety risks and ways of measuring risk, an epidemiological approach is recommended. A distinction is drawn between performance deficits, which are continuous in nature, and impairment, a legal term that refers to a cut-off that can distinguish groups of those who are a safety risk and those who are not.

CHAPTER 2

Alcohol and cannabis legislation and impairment assessment

TYPES OF ALCOHOL AND CANNABIS DRIVING LEGISLATION

Impairment also has a legal definition, which varies considerably from jurisdiction to jurisdiction. These legal definitions are reviewed in this Chapter. Worldwide, there are three major legal approaches for addressing alcohol or cannabis-impaired driving: (1) per se cut-offs, (2) behavioural methods and (3) zero tolerance.

(1) **Per se laws** establish cut-off thresholds of substance concentrations in biological specimens (i.e. either blood, urine, oral fluids or breath), and state that these are sufficient evidence that an individual is guilty of driving while impaired. No additional information on performance by individuals is needed for conviction. If drivers refuse to provide a biological sample demanded by police, they can be charged for impaired driving.

Per se laws are the most common approach worldwide for both alcohol and cannabis. These laws exist in North America and the European Union for alcohol, with many jurisdiction implementing BAC cut-offs of .05% or .08%. These cut-offs are consistent with research evidence that practically all people at this level show substantial performance deficits, and epidemiological studies indicate drivers at this level become a traffic-safety risk (Fell & Voas, 2014).

For cannabis, THC per se cut-offs are common in many countries and seven U.S. states (Wong et al., 2014). Most jurisdictions prescribe cut-offs based on whole blood although some prescribe blood ***serum***, urine or oral fluid tests. Concentrations cut-offs of

THC are most common. Some jurisdictions have zero tolerance laws (described more fully below) prohibiting the THC or the ***metabolite*** of THC, ***Carboxy-THC (THCCOOH)*** in drivers***.*** The strengths and limitations of these different biological specimens and the detection of different compounds are discussed more fully in subsequent Chapters. Typical per se laws forbid driving at thresholds between 2–5 ng/mL THC in whole blood or serum.

(2) **Behavioural criteria** laws to assess alcohol impairment based on performance measures rather than biological tests. Considerable efforts to operationally define these criteria have been made in North America with the development of the ***Standardized Field Sobriety Test (SFST)***, which can be used as evidence for Driving While Impaired (DWI) by alcohol offences in Canada (i.e. a Breathalyzer is not needed). The sobriety test includes three tests: the horizontal gaze nystagmus, walk and turn heel to toe along a straight line, and the one-leg stand. Failure on a certain number of components of these tests will result in being charged for alcohol impairment. Practically all sober people will pass this test, but inebriated people will fail, making it a valid test. In North America and most other countries, behavioural criteria can be used to convict drivers of impaired driving in addition to the per se laws.

Similarly, for cannabis and several other drugs, the ***Drug Recognition Expert (DRE)*** program, also called the *Drug Evaluation and Classification Program* (DEC) was implemented in Canada and many U.S. states (Beirness et al., 2007; Porath-Waller, et al., 2009). The process involves a series of physical and psychomotor tests and concludes with toxicological testing of a sample of blood, urine or oral fluid (Royal Canadian Mounted Police, undated). This standardized procedure is used to identify both individuals under the influence of drugs and the type of drug causing the observable impairment. Thus, the DRE process is a sequential testing approach (i.e. behavioural symptoms plus a drug test) as opposed to the behavioural criteria used for assessing alcohol impairment, which by itself is sufficient to be charged by police in Canada, although conviction is not certain.

A recent review paper of cannabis and driving legislation worldwide found that nine European countries have laws that include greater penalties for behavioural symptoms of impairment and lesser penalties for particular per se cut-offs, typically from THC concentrations in whole blood (Wong et al., 2014). Specific legislation exists in 16 European countries; 14 of these countries have legal THC limits of 2 ng/mL or below from whole blood or serum. In addition, three U.S. states reported legal THC limits in blood of 2 ng/mL or below. Canadian laws of the 2 ng/mL cut-off are therefore roughly in line with several other

countries. Whether or not these per se laws are consistent with existing scientific evidence is the focus of the next Chapters.

As mentioned, this system is not perfect for cannabis detection as mistakes occur. A question of importance is whether the Canada's 2018 laws are an improvement. How accurately will the laws be for identifying drivers who are a safety hazard? Will the laws make the roads safer? Will they be enforceable at both the police and judicial level?

(3) **Zero-tolerance** laws prescribe penalties at a threshold level of zero or the low levels of detection at which alcohol or drug can accurately be detected and can be thought of as per se laws that are not linked to performance criteria. For alcohol, a BAC of .02% is considered zero tolerance because research evidence does not show that a BAC level at .02% constitutes impairment, whereas, for cannabis, 1 ng/mL THC in blood is considered zero tolerance. Zero-tolerance laws are not premised on the presumption of impairment or any other subjective judgment about a driver's behaviour. Countries with cut-offs of .02% alcohol or below are considered zero tolerance. A few Eastern European countries, the Czech Republic, Hungary and Slovakia have absolute zero limits for alcohol. Other countries, such as Poland, Finland and Sweden, have limits of .02%, which allows for insignificant amounts of alcohol.

Six zero-tolerance countries in Europe and one U.S. state use THC limits of 1 ng/mL in whole blood or ***blood serum*** (Wong et al., 2014). Sanctions for cannabis users who drive are expected to reduce the likelihood of impaired cannabis driving and make the roads safer.

THE HISTORY OF ALCOHOL AND CANNABIS DRIVING LEGISLATION

Alcohol

Over 100 years of laboratory evidence shows that psychomotor abilities deteriorate considerably with the ingestion of alcohol. Increases in BAC levels are significantly related to decreases in performance (AMA Council on Scientific Affairs, 1986; Coambs & McAndrews, 1994; Jellinek & McFarland, 1940; McKim, 1986; Moskowitz, 1973; Moskowitz & Florentino, 2000). The question of importance was how to use this research to make the roads safer. Most legal interventions established in the early 1900s made impaired driving

an offence based on behavioural grounds of impairment. In the U.S., the first laws against drinking and driving were implemented in 1910 in New York. In 1939, Indiana introduced legislation that allowed evidence of BAC levels as corroborating evidence of alcohol impairment but had little value on its own. In Canada, the first criminal code legislation against drinking and driving was instituted in 1921. Initially, drinking and driving was penalized as a less serious ***summary offence*****;** it was not until many years later that it became an indictable (more serious) offence. In 1912, the first drinking-and-driving laws were implemented in Norway and several Scandinavian countries followed over the next two decades (Ross, 1975).

It wasn't until 1936 that the first per se law was implemented in and Sweden, using an early version of the Breathalyzer (Voas & Lacey, 1990). Although Robert F. Bornkenstein often is credited with inventing the Breathalyzer that assesses BAC, the first devices using breath tests to detect BAC date back to the 1870s (Wutke, 2014). The early science focused on developing an accurate breath sample that mirrored alcohol content in the blood. Studies showed that Breathalyzer readings corresponded very closely to performance deficits. The Borkenstein device, coined the Breathalyzer, was different from early prototypes in that it was portable, making it ideal for roadside use.

In 1964, at the same time as the Breathalyzer emerged, Borkenstein and his team conducted the first large scale, case-controlled epidemiological study that established a ***relative risk curve*** demonstrating an exponential relationship, starting at .08% alcohol, between BAC levels and crash risk (Borkenstein et al., 1964). This study, along with the Breathalyzer, paved the way for the first per se laws in North America, and made driving at a given BAC without behavioural grounds sufficient evidence for criminal penalties (Gore, 2010). Per se interventions for alcohol impairment greatly reduced alcohol-related collisions, described more fully in Chapter 7 (***Evaluation studies***).

In the late 1960s, per se laws were instituted in U.S. states and Canada for driving with a BAC of .08% alcohol or more, based on a Breathalyzer reading. In early years, only tests conducted at a police station were considered evidentiary. Traditionally in Canada, police were required to have reasonable grounds based on behavioural observations to demand a driver's breath sample (or a blood sample for those unable to provide a breath sample). Roadside breath readings are considered sufficient evidence for conviction. Over time, the penalties for drinking and driving became more severe and additional refinements, such as inclusion of penalties for refusing to take a breath test, were

introduced. In December 2018, the Canadian government enacted legislation to allow police to order a breath test without probable cause (Government of Canada, 2017a). Drinking-and-driving cases are the largest single-offence group, making up about 12% of all criminal charges, with about 53,000 drinking-and-driving cases heard every year in Canada (Kenkel, 2015).

Internationally, virtually every industrialized country has a per se law for alcohol. Per se legislative cut-offs are highly variable in different countries, ranging from 0% to .15%, with most countries applying limits of .05% to .08%. Lower limits in Scandinavian countries are likely related to the strength of ***temperance movements*** in these areas. In Sweden, a BAC of .02% is punishable as a criminal offence. Higher limits are noted in some U.S. states where alcohol use is widely accepted as a societal norm. Per se laws are confusing for some, as the amount of alcohol that different people can drink while remaining under BAC thresholds of .05% or .08% vary. This ***variability*** is based on the amount of ***ethanol*** consumed, body weight, metabolism, and time since last drink. An advantage of low per se laws (i.e. under .05% alcohol) is the simplicity of avoiding any drinking before driving. A drawback is that drivers at low BAC levels may be punished even though they do not necessarily represent a meaningful safety risk.

Laurence Ross, a prolific researcher who studied the impact of numerous per se legislations worldwide, noted positive short-term effects with their introduction (Ross, 1984). A more recent review of evaluation studies on countries that introduced or lowered legal BAC limits, confirms there are beneficial traffic-safety effects, at least in the short-term (Mann et al., 2001). Such research has helped galvanize social movements, such as Mothers Against Drunk Driving (MADD), which called for stronger deterrence-style legislation and increased funding to address this issue (Ross, 1984). Legislation then, and most worldwide legislation since, is based on the theory of deterrence***. Deterrence theory*** posits that the certainty, swiftness and severity of punishments for offenders will change unwanted behaviours (Ross, 1982; 1984). Ross found that perceived certainty of punishment was more effective than severity of punishment. Consistent with this conclusion, Norway and Sweden abandoned mandatory jail sentences for drinking and driving above certain limits (Ross & Klette, 1995).

In Canada and the U.S., there are limits to both the certainty and swiftness of punishment that can be achieved. Enshrined within the Criminal Code laws are the rights to due process, protection from unreasonable search and the right to defend oneself (Kenkel,

2015). The tenet that "beyond a reasonable doubt" is needed to convict someone of a criminal offence indicates that criminal conviction of an innocent person is worse than not convicting someone who is guilty. Furthermore, while criminal code laws mostly incorporate the principle of ***mens rea***, meaning that individuals must have criminal intent, this principle has been largely bypassed with per se laws. These factors impede the introduction of even tougher laws and are barriers to deterrence, as the judicial process is time-consuming. Substantial proportions of individuals charged under per se laws are never convicted. More leeway exists within provincial legislation, which mandates traffic safety and is guided by principles of public health more than individual rights. Most provinces have penalties for driving at a BAC of .05%, with penalties less severe than those under the Criminal Code of Canada but fewer safeguards for due process. Total abstention from alcohol is required for young/novice drivers and ***alcohol ignition locks*** are common in provinces for previously convicted drivers. British Columbia, for example, introduced a separate set of laws for drinking drivers known as the Immediate Roadside Prohibition Program, laws that are not feasible at a federal level. This provincial policy essentially bypassed the Criminal Code of Canada, as police could immediately suspend driver's licences for three days among drivers with BAC levels between .05% and .08% alcohol (Macdonald et al., 2013). The policy was found to be effective in reducing three types of alcohol-related collisions over a two-year period.

Implicit differences exist for the purposes behind criminal laws for impaired driving governed by Canada versus traffic safety laws governed by the provinces. Aside from the main purpose of deterrence in criminal laws related to impaired driving, three other purposes are sometimes mentioned: rehabilitation, protection of society and retribution. Rehabilitation typically involves education aimed at changing the behaviours of those apprehended. Protection of society typically involves confinement of offenders in prisons, where they are unable to commit crimes. Retribution involves punishment in return for a specific wrong. The expression an "eye for an eye" is an example of retributive goals. Those personally touched by the tragedy of being victimized by impaired drivers sometimes want retribution or prison time for the perpetrator and can influence judicial sentencing for a particular case. Unfortunately, these different purposes are often intertwined with one another, making it difficult to untangle the overarching purpose of criminal laws. Provincial laws for traffic safety are governed more from a public safety perspective. In this respect, provincial laws are more likely to be rooted in principles of deterrence and rehabilitation.

Overall, the bar or threshold for provincial laws is lower for the provinces than the federal government. Unjust convictions are more acceptable under provincial laws where the ultimate goal is safety for citizens as a whole.

Since per se limits vary so widely among countries, from zero to .15% alcohol, a question of importance is what cut-off is optimal. A low cut-off of .02% or less sends a clear-cut message that no alcohol in the blood is acceptable while driving (Klette, 1983). Although the Swedish will staunchly defend their laws and much of the public support it, their effectiveness in preventing alcohol-related crashes compared to higher limits of .05–.08% alcohol has not been clearly established (Klette, 1983; Ross, 1975). However, the preponderance of the research evidence does indicate lowering per se cut-offs, typically from the .08–.10% range to .05% alcohol, produces beneficial safety effects although they may be temporary, as there is a tendency for drivers to acclimatize to new laws and revert to old habits.

Cannabis

As was the case with alcohol a hundred years ago, many logistical issues related to the development of effective interventions against impaired driving by cannabis are being grappled with today. In Canada and the U.S., it is illegal to drive a vehicle while impaired by cannabis; however, to determine when drivers are actually impaired by cannabis is much more difficult than for alcohol. In Canada and most U.S. states, convictions are based on behavioural grounds of drug impairment (discussed in more depth in this Chapter), which are difficult to prove.

Legalization of cannabis in Canada brings new penalties for drivers with THC concentration in whole blood. These are:

- 2 to 5 ng/mL → summary conviction/offence
- Over 5 ng/mL → indictable offence
- BAC over .05% alcohol and over 2.5 ng/mL → indictable offence

Legislation in Canada will permit roadside oral fluid tests when law enforcement officers reasonably suspect that a driver has used cannabis (Government of Canada, 2017a). This policy may be expanded to include suspected use of other drugs as well. A positive

saliva sample would allow officers to demand a blood sample to conduct an evaluation for THC concentration.

Above, I have reviewed legislative approaches for alcohol or cannabis-related driving. Such legislation can be assessed on empirical grounds, if the purpose is to determine limits where drivers can be considered a traffic-safety risk. This can be achieved from laboratory studies that assess the validity of biological tests, observational studies in the real world on the relationship between cut-off levels and crash risk, and evaluation studies on the implementation of laws using cut-offs.

THE VALIDITY OF BIOLOGICAL TESTS

Central to epidemiology is the assessment of diagnostic tests to classify people into groups. Biological tests to assess impairment offer several advantages over tests using behavioural methods. They are more objective and easier to administer, and ideally, they can provide a single objective measure that is closely related to performance deficits at a magnitude known to be associated with increased crash risk.

Assessing the validity of biological tests is based foremost on the purpose for which the test is intended. Drug tests have been proposed for two different purposes: (1) to identify drug users, or those who have used cannabis and other drugs within specified time periods, and (2) to identify those who are impaired by drugs. The first purpose is concerned with detection of a drug concentration indicating drug use. The second purpose is the assessment of a particular drug concentration threshold to classify individuals as impaired, and is the focus of this book.

A valid test is one that correctly identifies people who are impaired (i.e. have performance deficits that increase safety risk) from those who are not. In order to accomplish this goal, we must have a good idea of how to define impairment. For alcohol, this has been achieved through countless laboratory and observational field studies. The laboratory studies show that virtually all people have measurable and meaningful performance deficits at .05% BAC (Fell & Voas, 2014). Also, field studies show the risk of crashes increases rapidly at BAC levels of .05%. Similar criteria for assessing the validity of blood THC can be applied to cannabis. After defining the meaning of impairment as an ***operational definition***, this ***gold standard*** can be used to assess the validity of a drug test

in laboratory studies. The gold standard is an external source of truth regarding the magnitude of deficits known to be associated with increased crash risk.

Validity of a drug test can be measured in several dimensions, as outlined by Gordis (2014) and illustrated in **Table 1**. ***Accuracy*** is defined by the sum of the correctly identified subjects with respect to impairment (i.e. true positives and true negatives) divided by the total sample. Two common measures are ***sensitivity*** and ***specificity***. Sensitivity is the ability of the test to identify correctly those who are impaired, whereas specificity refers to the ability of the test to identify correctly those who are *not* impaired. Two directly related indicators, ***false negatives*** and ***false positives***, are defined by the respective formulas of (1 – sensitivity) and (1 – specificity). Another important indicator is ***positive predictive value***, or the probability that someone who tests positive is truly impaired. The ***Kappa*** statistic is often used to assess the degree of agreement between a test and a gold standard. The ideal situation is a perfect test where all of the persons identified as impaired are truly impaired, and all those identified as non-impaired are truly not impaired. Regrettably, this ideal is unrealistic. A Kappa value of over .75 is optimal (excellent agreement). Scores between .4 and .75 are intermediate to good agreement and under .4 is poor agreement (Gordis, 2014).

Table 1: *Different indicators of validity of a biological test for impairment*

Test result at a particular cut-off	Impaired	Not impaired
Positive	True positive (TP)	False positive (FP)
Negative	False negative (FN)	True negative (TN)

Source: Adapted from Gordis (2014, p. 91)

Accuracy = (TP+TN)/ (TP+FP+FN+TN)
Sensitivity = TP/ (TP+FN)
Specificity = TN/ (TN+FP)
Positive Predictive value = TP/ (TP+FP)
Negative Predictive value = TN/(FN+TN)
Kappa = (Percent observed agreement – Percent agreement expected by chance)/ (100% – Percent agreement expected by chance).

Drug concentrations are detectable at various levels as a ***continuous variable*** and cut-offs are chosen to reflect a reasonable trade-off. Assuming that the drug concentration level bears some relationship to impairment, even a weak one, lower thresholds will increase false positives (reduce specificity) and decrease false negatives (increase sensitivity). Conversely, higher thresholds will decrease false positives and increase false negatives. If the consequences of false negatives are very great, then a lower threshold is

recommended, and if the consequences of false positives are great, then a higher threshold is warranted. The threshold chosen depends on the degree of importance placed on the consequences of the two types of errors. For alcohol and drug testing, this trade-off includes values of safety versus individual freedoms, the validity of the tests, and the effectiveness of the different interventions. As recommended by Wald and Bestwick (2014), a useful approach is to specify the acceptable sensitivity rate for a given specificity rate (or false positive rate). This issue is largely unaddressed in research. Typically, overall accuracy is acceptable if the Kappa value exceeds .75 (Gordis, 2014).

Ideally, assessment of the validity of a biological test for impairment should be made against a gold standard. This gold standard would typically be performance deficits associated with crashes. Unfortunately, as described in Chapter 5, performance deficits are measured in such a wide variety of ways that the precise definition is still largely undefined for cannabis deficits. Research on this topic is superior for alcohol compared to cannabis. Nonetheless, research has been conducted on assessing the validity of the field sobriety test battery against BAC levels and the DRE against positive or negative THC, reviewed below.

Alcohol

Laboratory-style studies have been conducted using the epidemiological approach to assess the validity of the Breathalyzer to detect impairment. Some of the early research was directed to develop more accurate psychophysical tests of alcohol impairment. This research recommended the one-legged stand, walk and turn and alcohol gaze nystagmus as the three most valid combined indicators of alcohol impairment. These direct measures of performance deficits caused by alcohol, the SFST can be thought of as the gold standard for impairment. The vast majority of people who are not inebriated would find these tests simple to pass and those inebriated would find them difficult.

Stuster and Burns (1998) assessed the validity of the SFST for alcohol impairment against a BAC threshold of .08%. Seven police officers trained in the behavioural approach rated 297 drivers on the road, according to a scoring system that estimated BAC levels. I rearranged the data from the Stuster and Burns (1998) study to be consistent with my epidemiological approach (see **Table 2**). I have assessed the validity of a BAC cut-off of .08% alcohol against expert behavioural symptoms. Overall, a BAC cut-off of .08% alcohol is valid

compared to SFST. Positive predictive value is excellent at 98%, meaning a driver with a BAC of over .08% has a 98% likelihood of being judged impaired by the SFST. The Kappa value is .75, indicating excellent agreement. Specificity, at 94%, is greater than 90% for sensitivity, which corresponds to a larger percentage of false negatives than false positives. Findings from this study provide evidence of excellent validity of .08% alcohol for impairment.

Stuster and Burns (1998) also compared officers' assessments with BAC cut-offs below .04% alcohol with those between .04 and .08% alcohol and calculated accuracy at 80%. Based on this data, I calculated Kappa at .36, indicating poor agreement. Unfortunately, all the cases above .08% alcohol and others are missing from the table, and I was not able to replicate the table for a simple .04% cut-off. However, from the information available, the level of agreement between officers' assessments of a .04% cut-off with BAC cut-offs declines considerably into the unacceptable range.

Table 2: *The validity of .08% BAC cut-off compared to Standardized Field Sobriety Tests*

	SFST assessment for a 0.8% cut-off		
.08% cut-off	**Impaired**	**Not impaired**	**Total**
Positive	210	4	214
Negative	24	59	83
Total	234	63	297

Source: Adapted from Stuster and Burns (1998).

Accuracy = 91%
Sensitivity = 90%
Specificity = 94%
Kappa= .75

Positive Predictive value = 98%
Negative Predictive value = 94%

Burns and Anderson (1995) compared police decisions to arrest those for impaired alcohol driving in Colorado with BAC cut-offs of .05%. Results from this study are presented in **Table 3** with an analysis of the validity. As can be seen from the table, the Kappa value drops to the moderate range at .61 when compared to Stuster and Burns (1998). Specificity declined fairly substantially. Sensitivity increased, consistent with expectations with a lower threshold compared with a higher cut-off of .08% alcohol (shown in Table 2 above). My overall assessment is that per se laws at .05% have a moderate degree of validity. Based on these findings, criminal code per se penalties at .05% alcohol are less justified than current per se laws of .08% alcohol, based on the purpose of the criminal code; however, lesser

penalties under provincial legislation or summary convictions without criminal records based on a public health approach are more justifiable.

In another study, Stuster (2006) compared police observations based on SFST (the gold standard) with BAC cut-offs at .08% alcohol. They calculated Kappa values for each of seven police officers with values that ranged from .61 to 1.0, indicating intermediate to excellent agreement. The findings of this study along with the large body of additional laboratory studies comparing BAC levels with performance indicators (reviewed in Chapter 5), do indicate current BAC cut-off levels of .05% and .08% to determine impairment are justified in North America.

Interestingly, all the aforementioned studies indicated their purpose was to validate the SFST, and not a particular BAC cut-off. In other words, BAC was treated as the gold standard of impairment rather than SFST. This observation indicates how entrenched BACs have become a valid indicator of impairment. BAC is a biological measure that is used for convenience and expediency and as such should be validated against external gold standards of impairment. The SFST represents the best behavioural measure of alcohol impairment and preceded common use of BACs. In any case, research indicates that BAC cut-offs of .05% and .08% have validity when using SFST at the gold standard of impairment.

Table 3: *The validity of .05% BAC cut-off compared to Standardized Field Sobriety Tests*

	Behavioural assessment of .05% cut-off		
.05% cut-off	**Impaired**	**Not impaired**	**Total**
Positive	163	21	184
Negative	12	38	50
Total	175	59	234

Source: Adapted from Burns and Anderson (1995)

Accuracy = 86%
Sensitivity = 93%
Specificity = 64%
Kappa= .61

Positive Predictive value = 89%
Negative Predictive value =76 %

Cannabis

The Drug Recognition Expert (DRE) program, also called the Drug Evaluation and Classification Program (DEC) program, uses a 12-step procedure to assess cannabis impairment, which represents our best measure to date; however, it is inferior to the SFST for alcohol. Biological drug tests have been used to assess the validity of the DRE approach. This approach is much less valid for cannabis impairment than for alcohol. The DRE process includes 12 steps involving clinical measures, such as blood pressure, pulse and pupil size which are not focused on behavioural impairment and have not been properly validated. Although some clinical signs, such as elevated blood pressure and pulse, may be more common among those with cannabis impairment, these conditions are common among those without impairment and appear to be poor measures for cannabis impairment. Other steps are more directly focused on performance, such as the finger-to-nose and modified Romberg balance test, indicators of divided attention. These divided-attention tests appear to be fairer criteria to classify individuals as roadworthy. Research is needed to assess whether drivers who do not pass these tests have the necessary skills for safe driving. This type of abbreviated approach is one that could be considered as an intervention approach by the Provinces. If a gold standard of cannabis impairment is to be achieved, it will be through the development of indicators of direct performance measures, and ideally, signs that are specific to cannabis impairment. The final step is a drug test with blood, oral fluids or urine, which is also a poor biomarker of performance deficits that could be considered impairment, as demonstrated in Chapter 3 of this book.

In a review of the validity of the DRE program based on both laboratory and field studies, Beirness et al. (2007) identified nine studies that implemented an epidemiological approach for the validity of DRE officers' assessment for identifying drivers under the influence of drugs. However, all the studies were limited in that they compared DRE assessments with drug tests that are unproven to show impairment. In four of these studies, subjects were administered cannabis and DRE assessments were made of behavioural indicators of impairment. We do know that, for most people, the acute effects of cannabis produce deficits that make driving a car unsafe (as shown in other sections of this book). In laboratory studies, subjects were administered both cannabis and ***placebos*** under highly controlled experimental conditions and subjects were tested shortly thereafter, when impairment is likely (although some studies used very low doses). Although Kappa values were not reported by Beirness et al. (2007), overall accuracy, sensitivity and specificity are

reported to assess validity. As shown in **Table 4,** the accuracy of identifying those who were administered cannabis is better than chance, but poor overall, ranging in accuracy from 39.7% to 63.6%. These studies do not inspire confidence that the DRE approach is valid for accurately detecting impairment, given the controlled conditions of the laboratory studies.

In field studies in real-world conditions, DRE assessments were compared to toxicological findings that were either positive or negative, based on urine, oral fluid or blood tests. These studies are flawed because we don't know if these biological measures had any valid relationship with impairment, a limitation identified by Beirness et al. (2007). Based on what we know about these drug tests, the studies determined whether the DRE assessment was valid to detect use, not impairment. Noting that accuracy rates were better for field studies than laboratory studies, Beirness et al. (2007) speculated that police officers had the benefits of gaining additional information from an initial investigation and that the dose may be greater in real-life field settings compared to laboratory doses. Although these explanations are reasonable, the DRE assessment in all the field studies were compared against biological tests, which detect prior use (not necessarily currently under the influence), whereas in all the laboratory studies, cannabis was administered shortly before assessments when being under the influence is likely. Higher accuracy rates in field studies could also be related to the detection of users rather than those impaired, whereas the laboratory studies were more specifically aimed at detecting those under the influence.

Regardless of these aforementioned limitations, only one study (Hardin et al., 1993; reported in Beirness et al. 2007) produced indicators of validity (i.e. accuracy, sensitivity and specificity) that were even close to the study by Stuster and Burns (1998) for alcohol impairment. The DRE protocol is not a scientifically valid technique for proving that an individual has consumed a particular class of illicit drug resulting in impairment (Smith et al., 2002), but officers are able to identify drug classes with an accuracy better than chance (Beirness et al., 2007). Nonetheless, an advantage of the DEC approach is increased specificity and fewer false positives, (Gordis, 2014) because ***sequential tests*** are used rather than compared to a single measure. Sequential tests are more appropriate for diagnostic than screening purposes. The DEC process is cumbersome for charging suspected drug-impaired violators, and another drawback is a low conviction rate for drug-related charges (Solomon & Chamberlain, undated).

Table 4: *Accuracy, sensitivity and specificity of DRE assessment with biological tests*

Author	Accuracy (%)	Sensitivity (%)	Specificity (%)	Type of test	Lab or field study
Bigelow et al., 1985	63.6	48.8	92.7	Drug administered	Lab
Heishman et al., 1996	56.0	53.1	61.1	Drug administered	Lab
Heishman et al., 1998	39.7	30.4	59.1	Drug administered	Lab
Shinar & Schechtman, 2005	41.7	49	69	Drug administered	Lab
Compton, 1986	74.6	59.7	86.4	Blood	Field
Preusser et al., 1992	75.4	78.4	73.2	Toxicology reports	Field
Hardin et al., 1993	90.1	93.8	82.6	Urine	Field
Smith et al., 2002	79.9	80.5	76.6	Toxicology reports	Field

Source: Adapted from Beirness et al. (2007)

In a similar study by Beirness et al. (2009), actual DRE evaluations and toxicology reports were compared. The authors concluded the DREs in Canada are accurate in that DRE substances matched toxicological reports cannabis use in 87.3% of the cases. Similar to limitations of the 2007 study, we cannot say whether the subjects were unsafe to drive – only that they met the criteria of impairment under Canadian laws. The authors note that subjects are asked about recent drug use for investigations, which can have an influence on decisions. Also, the authors do not know whether they received a comprehensive list of all DRE cases. Other studies have assessed the validity of various aspects of cannabis impairment but none were found that used the epidemiological methods that I propose.

In a study by Papafoutiou et al. (2005), the authors assessed a modified SFST that included an additional performance test of head movements compared against time points after cannabis administration at five, 55 and 105 minutes. Behavioural assessments of impairment were best at five minutes after use in the high-dose condition (56.4% classified as impaired) and declined after 105 minutes (38.5% classified as impaired). This study only focused on sensitivity (not specificity or overall validity) and direct comparisons were not made with blood tests, so the study is of marginal value for understanding the validity of

blood tests. No studies were found where behavioural symptoms of impairment were compared directly with THC blood test cut-offs intended to assess impairment.

As well, Bosker et al. (2012) examined the SFST among occasional and heavy cannabis users, administered two doses of Dronabinol and a placebo. No differences were found between groups.

Hartman et al. (2016) compared 302 DRE cases of those with confirmed impairment based on DRE symptoms with 302 non-using controls on a number of measures. These measures included the modified Romberg balance test, walk and turn, finger to nose and one-leg stand. These tests aim directly at performance deficits related to cannabis impairment and normally non-impaired people should find them easy to pass. Sobriety tests can have greater validity when the test relates directly to one's ability to drive a car. In this respect, the common sobriety test of the one-legged stand and walking a straight line toe to toe appears to be an excellent measure of driving capability. These tasks are exceedingly simple to complete for most sober people. However, when intoxicated, they become difficult. Hartman et al. (2016) also tested several physiological symptoms, such as pulse, systolic blood pressure and pupil size. Several variables significantly distinguished the two groups; however, such measures do not appear to have good validity as they are very indirect measures of use, and do not necessarily indicate performance deficits. Although this study is useful for identifying variables that can be used to identify cannabis impairment, no differences in measures were found among cases with blood THC above 5 ng/mL and those below, a finding that doesn't support the hypothesis that THC cut-offs in blood are a valid indicator of impairment. Another study reported similar findings where Field Sobriety Tests were useful in detecting cannabis impairment but blood tests for THC were not (Declues et al., 2016). This study suggests a single THC per se limit of 5 ng/mL in blood will not have good validity.

Ginsburg (2019) conducted a review of the literature on the relationship between THC doses and standard deviation of lane position (***SDLP***). SDLP is a common measure of weaving when driving. The authors did find increased SDLP associated with increased THC doses based on an examination of seven studies.

CONCLUSION

In this Chapter, studies that assess the validity of tests for alcohol and cannabis impairment were reviewed. Research shows that a BAC threshold of .08% has excellent validity against objective behavioural symptoms, such as the SFST, and a BAC cut-off of .05% has moderate validity. As BAC levels decline, the validity of SFST becomes much less reliable to discriminate those who have consumed alcohol from those who have not. For cannabis, the 12-step DRE approach has good accuracy against biological tests in field studies, and poor validity against administered THC doses (Beirness et al., 2007). If DRE assessments are considered the gold standard for impairment, they have not been validated against a reasonable threshold for impairment using any type of biological test. Most of the 12 steps for the DRE approach do not identify behavioural symptoms of cannabis impairment, and have many steps that need to be administered in controlled settings. These factors make the DRE impractical as an effective intervention approach.

The modified Romberg balance test, walk and turn, finger to nose and one-leg stand are valid screening tools for police officers in the field to screen for alcohol impairment. However, symptoms of cannabis impairment are very subtle and difficult to detect, especially with psychomotor skills. Since symptoms of being impaired by cannabis are difficult to detect, an implication is that driving under the influence of cannabis may not be as hazardous. As demonstrated in this book, much of what we know about alcohol-impaired driving and detection cannot be applied to cannabis-impaired driving. I compare our scientific knowledge of alcohol with cannabis on issues related to performance deficits and how to detect them throughout this book.

Thresholds for cannabis impairment should be validated with experimental studies and this has not been done. There are major gaps in the literature, as no studies were found where behavioural symptoms of impairment were compared with a threshold above the limit of detection to assess the validity of any THC cut-off using a standard epidemiological approach.

CHAPTER 3

Detection approaches for alcohol and cannabis

ANALYTIC METHODS

Alcohol

The main method of detecting BAC levels is with portable Breathalyzers. These devices are typically based on an infra-red and/or a fuel cell device (Wigmore, 2014). Breathalyzers are considered to give highly accurate approximations of BAC levels, as outlined below, although they are not perfect. For example, to be valid, subjects should not have anything to drink at least 10 minutes before the test and must be able to provide a full breath sample.

Cannabis

Several analytic methods exist for the detection of prior cannabis use, but two major approaches deserve special attention: *screening* and *confirmatory* tests. Screening tests, based on an ***immunoassay*** procedure, use antibodies to detect the presence of drugs and their metabolites (Dyer & Wilkinson, 2008). These immunoassays generally lack accuracy to detect a specific type of compound. Rather, they detect several types of compounds that have similar molecular structures, but the combination and concentration levels of each compound are unknown. A major limitation of these screening tests is reduced accuracy. Screening tests are used due to their lower costs and results that can be quickly obtained

and interpreted on-site. Canadian legislation for driving under the influence of cannabis includes oral fluid screening tests.

A key challenge with respect to field testing novel methods is the validity, expense, time and portability of different analytic tools. The immunoassay approach can provide rapid results within minutes and without a laboratory. Additionally, the immunoassay approach is relatively inexpensive and highly portable. A major limitation is their lack of validity for impairment. The confirmatory approaches with ***chromatography and spectrometry*** methods generally have excellent validity but require more expensive non-portable laboratory equipment and time-consuming analysis.

Confirmatory tests are near perfect for detection and identification of specific drug compounds and use chromatography and spectrometry methods (Jaffee et al., 2008). These methods are often used to compensate for the inaccuracy of immunoassays approaches. To analyse urine, gas chromatography and mass spectrometry ***(GC/MS)*** are typically used, whereas oral fluids are analyzed using liquid chromatography and tandem mass spectrometry ***(LC/MS/MS)***, methods that are treated as equally valid. As mentioned, these confirmatory approaches effectively identify single compounds, such as THC, but require more expensive non-portable laboratory equipment and analysis is time-consuming. The validity of these tests relates to detection of concentration levels of the compound or metabolite being targeted, not behavioural symptoms, such as being under the influence of a drug. Validity regarding how concentration levels relate to impairment is discussed in later Chapters.

SUBSTANCES DETECTED

In the material below, I focus my review on the elimination rate of various drugs based on drug concentration levels. These estimates are derived from ***controlled dosing studies*** where subjects are administered drugs and concentration levels of different chemicals in the drug are measured at different time points.

Alcohol

The Breathalyzer is designed specifically to detect ethanol, the single-molecule of alcohol, C_2H_5OH.

Cannabis

Drug tests for cannabis can be used to detect the presence of various compounds and metabolites. Cannabis is extremely complex, with over 400 different compounds, many with psychoactive properties (Adams & Martin, 1996; Atakan, 2012). The main psychoactive component of cannabis is delta-9-tetrahydrocannabinol (THC), which has been most studied and the most promising compound to choose as a cut-off in relation to impairment. ***Carboxy-THC*** (THCCOOH), a THC metabolite, is typically detected with urinalysis and used to identify drug users rather than those impaired. Like THC, carboxy-THC can be stored in fat cells for days and possibly weeks in heavy daily users. ***Hydroxy-THC (11-OH-THC)*** is another major psychoactive metabolite of THC. Compounds and metabolite concentrations are typically expressed in nano-grams per millilitre (ng/mL). The focus of this book will be mainly on the detection of THC and these metabolites. There are other psychoactive components in cannabis, identified by Sharma et al. (2012), but little research has been conducted on their impact on performance. Another component in cannabis, ***cannabidiol (CBD)*** has been widely researched for its medicinal effects but is not psychoactive, and cannot be considered a viable biomarker for impairment. Some people believe that CBD modifies performance deficits from THC. A more recent study indicates cannabis with high CBD and THC content (11%) lane weaving was not reduced by CBD (Arkell et al., 2019). A larger literature review concluded the finding of empirical studies are mixed on whether CBD modifies the effects of THC (Freeman et al., 2019). It appears that if CBD modifies the effects of THC, these effects are modest.

SUMMARY STATISTICS AND CORRELATIONS

In this section, I provide a description of different types of statistics relevant to drug testing and their use. The material in this section is comparable to what is taught at an undergraduate statistics course. It is intended for those who have little education on this subject.

The importance of measures of dispersion

In reviewing the controlled dosing studies, various types of summary statistics are presented by authors. Summary statistics are useful to provide simpler understanding of

the sample distributions. Measures of ***central tendency*** (mean, median and mode) and measures of ***dispersion*** (***standard deviation, coefficient of variation (CV),*** and range) are common descriptors. In controlled dosing studies, measures of dispersion have more relevance than central tendency for the purpose of using drug tests to discriminate those impaired from unimpaired. Measures of dispersion provide more insight into accuracy of the tests and are related to validity estimates of sensitivity and specificity. Measures of central tendency by themselves can obscure differences between individuals.

In controlled dosing studies, subjects are typically administered the same amount of cannabis and therefore should have similar THC concentrations at different time points after use. Yet large differences exist between individuals or within the same individual over time — sources of error that indicate the impracticality of drug tests to detect impairment. The reasons for these large variations are largely unknown. In the following material, I provide an interpretation of different summary statistics.

When interpreting the degree of dispersion in a sample, I examine three primary measures: standard deviation, coefficient of variation and range of the sample. I look at the standard deviation to better understand the dispersion of a sample. When a distribution is normally distributed, about 68% of the samples are within plus or minus one standard deviation from the mean. However, in controlled dosing studies, the distribution of concentration levels is always positively skewed (i.e. a few subjects with very high THC concentrations and a large proportion with low concentrations) and sometimes the standard deviation is greater than the mean. If you subtract the standard deviation from the mean in some instances, you will end up with a negative number. This means that the concentration levels above the mean are much further apart than those below the mean. The size of the standard deviation in relation to the mean provides a useful of the dispersion of a sample and is also the definition of CV.

The CV of a sample is a universal measure that provides a measure of dispersion so that variables with different units of analysis can be compared easily. Thus the CV can be used to compare the dispersion of compounds from drug tests of blood, urine and oral fluids. The CV is calculated by dividing the standard deviation of the sample by the mean. If the standard deviation is extremely small in relation to the mean (i.e. under 5% the size of the mean) the dispersion of the sample is very low. If the CV is extremely large, the degree of variability of the sample extremely high. **Table 5** provides a ballpark interpretation of the CVs in terms of dispersion. When the standard deviation is larger than the mean, I typically

interpret this observation as an indication the sample is highly dispersed. Larger dispersion in the sample, such as drug concentrations, is related to a lower likelihood a diagnostic test will be valid. Simply put, the larger the degree of variation of drug test concentrations between subjects, the lower the likely utility of the test as a diagnostic tool. The reasons for the variability need to be understood in order for the test to have practical utility. The very large variations in THC concentration levels between people are likely due to several factors, not just one or two factors. If a cut-off is chosen to classify people who are impaired, this variation between people will translate into higher levels of error (i.e. misclassification). By comparison, only a few factors are related to BAC with body weight as the most important. As well, the elimination of alcohol from the body is fairly constant from person to person. The CV can be thought of as a measure of ***reliability*** of a measure – lower dispersion is associated with increased precision of estimates.

Table 5: *Interpretation of coefficients of variation (CV)*

Coefficient of variation (CV)	Degree of variability
Under 5%	Extremely low
Between 6–20%	Low
Between 21–85%	Average
Between 86–95%	High
Over 95%	Extremely high

Note: CV = standard deviation/mean

Correlations

Another statistical test introduced in this Chapter is linear ***correlation***, which is assessed with a ***correlation coefficient (r)*** and ***coefficient of determination (r^2)***. In linear correlation, a straight line of best fit is plotted based on minimizing the distance between all the data points. Other types of lines, such as curves can also be calculated but are less commonly used. ***Statistical significance***, determined by probability (p) values, provides an objective measure of the likelihood that a relationship is caused by something other than random chance. The p-value is related to both the sample size (i.e. number of subjects) of a study and the variability between measures. Virtually any relationship, no matter how weak, can be significant with a large enough sample; however, it does not mean that the significant relationships are necessarily meaningful. Tests of statistical significance are

necessary to demonstrate a relationship, but such tests are not sufficient to say the relationship is good, moderate or poor.

Correlation coefficients (r), are used for comparing two continuous variables and range from -1 to 1 with a plus or minus sign, which represents the direction of the relationship. A coefficient of determination (r^2) provides an objective means to define the strength of relationships between two continuous variables (i.e. ***effect size***). If the purpose of the correlation is to demonstrate that one measure is valid against another measure, such as between oral fluid and blood THC concentrations (or between blood alcohol content and Breathalyzer tests for alcohol), r^2 can be interpreted in the same way as Kappa coefficients if the purpose of the test is to substitute one type of measure for another (i.e. .75 is excellent, between .4 and .75 is intermediate and under .4 is poor). The r^2 value has more intrinsic meaning than a correlation coefficient (r). When r is squared, it can be interpreted as the percent of variation in one variable that is shared with a second variable. If the purpose is to show that a strong relationship exists between two variables, such as THC blood levels and performance deficits, then less stringent criteria are needed than for substituting one type of test for another. As a general guideline, an r^2 value of .5 or higher is desirable. Some studies of the relationship between BAC levels and performance deficits exceed this threshold (see Dawson & Reid, 1997).

When assessing whether a statistical relationship is meaningful, it is important to take note of both the statistical significance and the effect size. The probability value is the likelihood that a given strength of a relationship is due to chance, and for this value to be significant, it should be below 5%, or $p<.05$. The likelihood of ***probability values*** being significant is based on both the sample size and the variability in the measures. If statistical significance is achieved, then it is useful to examine the effect size of a relationship to see if it is meaningful, given the purpose of the test.

An assumption of correlations is that all observations are independent of one another (i.e. assumption of ***independent measures***). In some controlled dosing studies, multiple repeated measures of the same individuals were used to calculate a correlation coefficient. This procedure is incorrect and will produce inflated correlation coefficients, giving a distorted impression that the relationship is stronger than reality. This inflation occurs because the variability among pairs of observations of the same individuals is more consistent than those between different individuals. If researchers have done this, it is best to disregard the paper because the findings cannot be interpreted properly.

DETECTION PERIODS FOR DIFFERENT BIOLOGICAL SAMPLES

Controlled dosing studies, where subjects are administered substances and THC concentration levels are measured at different time intervals after use, provide useful data on the drug concentration elimination rate and detection periods over time. Knowledge of elimination rates can provide only a rough approximation of concentration levels associated with typical impairment periods. In the following Chapter, I compare the typical impairment periods for alcohol and cannabis with the concentration levels. In subsequent Chapters, I review studies of paired detection tests and performance measures.

Various biological samples can be analysed for the presence of cannabinoid compounds: blood, breath, oral fluids, urine, sweat and hair. Sweat testing and hair testing are not reviewed in detail here. Briefly, hair testing is suitable for assessing exposure to drugs for up to 90 days. Sweat testing is typically used for monitoring drug use (through a transdermal patch) over extended periods of time (Cone et al., 1994).

Differences exist among biological sample types in relation to what can be learned from the test results, especially when detecting performance deficits and impairment. Detection periods for specific compounds vary enormously based on the type of biological sample. For most compounds, the detection periods are the shortest in blood, and longest in hair. Oral fluids have shorter detection periods than urine. Since performance deficits from the acute effects of drugs are short-lived, blood tests are frequently cited as the best matrix to assess impairment for all substances. It is important to note that a specific concentration level in one biological sample is not equivalent to that in another type of biological sample. The concentration level of compounds and metabolites between different samples vary considerably for individuals at the same point in time. For example, oral fluids generally contain many time's higher concentrations of THC soon after use and decrease over time, compared with blood samples from the same person (Lee et al., 2013).

In the next section, I describe the detection periods for alcohol and cannabis in blood, breath, urine and oral fluids, with a focus on elimination rates in the different biological samples and the validity of alternative samples to blood.

TYPES OF BIOLOGICAL SAMPLES

Alcohol

Blood—Blood tests are considered the best biological sample for assessing blood alcohol content or BAC (Lindberg et al., 2007); however, even with blood tests, readings can be misleading in certain situations. Misleading results can be obtained from diabetics, and in those taking certain cough medicines or certain herbal supplements.

Blood is analysed as three major mediums: (1) ***whole blood***, (2) ***serum*** or (3) ***plasma.*** Serum and plasma are obtained by centrifuging a whole blood sample into its constituent parts. Serum and plasma are more common in medical facilities, whereas whole blood is typically mandated for legal purposes. In drinking-and-driving cases, blood samples of injured drivers can be taken for medical reasons and can later be subjected to subpoena by police, and it is important to understand the difference. The ratio between alcohol in serum/plasma and whole blood is fairly consistent. Rainey (1993) reported 12 empirical studies on this issue, with a mean ranging from 1.10 to 1.21. Rainey (1993) calculated that 99% of the population would have a ratio of .90 to 1.49. The low standard deviation and low range in ***conversion factors*** indicate moderate variations between individuals.

The elimination rate of ethanol for an average individual is about .016% absolute alcohol per hour, or between one half and one standard Canadian drink per hour (Andreasson et al., 1995). The rate of alcohol elimination from the blood for a given individual is very constant.

Breath—Breath tests were the first test developed for detection of alcohol and are advantageous given they are more convenient and less intrusive than drawing blood. In order to assess their validity, studies have been conducted that compare blood and Breathalyzer tests for subjects who have consumed various amounts of ethanol. Alcohol is much more concentrated in the blood than in the breath. In a laboratory study conducted with 799 subjects, the average concentration of alcohol in blood compared to breath was 2407 to 1 (95% ***Confidence Interval (CI)***: 1981–2833) (Jones & Andersson, 1996), indicating low variability between-subjects. More recently, Jaffe et al. (2013) conducted a study that addressed issues of potential measurement bias in prior studies. The study included 61 subjects with paired blood/breath alcohol content measures. Treating blood as the gold standard with a cut-off of .05% BAC, breath tests had high sensitivity (97%) and specificity

(93%). The blood/breath ratio of alcohol on average is about 1 to 2400, but is not a constant factor both between and within individuals over time (Jones, 2010). In order to compensate for errors in conversion and the fact that the ratio increases over time, Canadian laws have adopted a conservative ratio, which means BAC calculated based on breath alcohol results is lower than the actual BAC measured in blood.

Overall, extensive research has been conducted that demonstrates portable breath test findings are closely correlated with blood tests. Alcohol breath readings have been validated against blood concentration through statistical calculation of correlations between the two from paired readings of different subjects. An example of findings from one study of suspected impaired drivers by alcohol is provided (Zuba, 2008). The coefficient of determination (r^2) in this study was .88. Breath concentrations accounted for 88% of the variation in blood readings and indicates a strong relationship that validates the Breathalyzer as an acceptable alternative test for a blood test (see Chapter 7, Strength of association, for interpreting r-values). A similar study by Gainsford et al. (2006) of four different Breathalyzers found nearly identical relationships. Findings similar to these have been found in several other studies. The Breathalyzer, while not perfectly accurate, is an excellent substitute for blood tests.

Oral fluids—Oral fluids can also be tested for alcohol and are reported to have a near-perfect correlation (r=.98) with blood tests (Haeckel & Peiffer, 1992). The feasibility of using oral fluid tests was established over 20 years ago through ratios for oral fluid and blood concentrations that demonstrated extremely low variability between individuals (***coefficients of variation*** (CV) between 3.2 and 4%) (Jones, 1995). Oral fluid tests offer a good alternative for individuals who are unable to provide a breath sample, as these tests are not highly invasive. Alcohol detection with oral fluid tests is gaining interest, as they can be used to detect alcohol and several other drugs simultaneously.

Urine—Urine tests to detect alcohol are much less accurate than breath and blood tests for BACs. One limitation of urine tests is that people can be experiencing the effects of alcohol but alcohol is not be detectable in urine for up to two hours after drinking. This is especially problematic for assessing impairment. Another issue is unacceptable variations between individuals for the urine/blood conversion, which was studied several decades ago (see Payne et al., 1967 for a review). The British Medical Association recommended a conversion factor of 1.32/1 once the peak concentration level had been passed. The range

between individuals' urine/blood ratio has been found to be from .92 to 2.32, indicating poor agreement.

In conclusion, although alcohol can be detected easily in urine two hours after drinking, accurate estimation of BAC levels cannot be made. Considering the invasiveness of urine collection (compared with breath tests) and its poor accuracy, urine tests are rarely used. Other biological samples such as sweat and eye vapours have been studied as possible specimens for impairment, but are not widely used.

Cannabis

In this section, studies of detection times for different biological specimens are reviewed, including urine, oral fluid, sweat, breath and blood. Since detection times vary dependent on the cut-off, I focus on studies in this section that took exact concentration levels after use. Since THC is the main psychoactive ingredient of cannabis and the acute effects of cannabis are short-lived, THC is the most studied compound as a possible biomarker for impairment. For an overview of the advantages and disadvantages of different biological specimens, including sweat and hair for drug testing, see Compton (2017). The detection time (i.e. the time from last use to the test) for THC and all drugs varies among individuals, regardless of the testing technology, depending on the dose taken, frequency of use, route of administration, duration of use, tolerance, metabolic rate and cut-off levels of the tests (Dyer and Wilkinson, 2008; Verstraete, 2004). Positive drug tests can result from licit sources as well as illicit use. For example, a positive test for cannabis could be due to pharmaceutical THC (Sativex) (Cone & Huestis, 2007) or over-the-counter hemp oil products (U.S Department of Transportation, 2004).

Blood

There is strong agreement among experts that blood tests are the most valid for detection of THC concentration levels associated with impairment for cannabis (Lindberg et al., 2007; Wolff et al., 1999). If the purpose of the sample is to assess a safety risk, blood is the best specimen. However, drawing blood requires specialized training, is invasive and the blood needs to be analysed by laboratories. As well, blood needs to be taken almost immediately when impairment is suspected. Blood tests have the shortest detection period compared to all other types of biological samples.

Three types of blood samples are possible: whole blood, serum and plasma. Research shows that the ratio of THC concentration in serum/plasma to whole blood from the same individual differs greatly, depending on the time point after use. Concentration levels are thought to be roughly equivalent for serum and plasma. Both of these specimens contain higher drug concentrations of THC than whole blood. Furthermore, empirical evidence suggests that whole blood/plasma ratios vary considerably between individuals. For example, Schwilke et al. (2011) found significant differences (p=.003) in the whole blood/plasma THC ratios between subjects. Desrosiers et al. (2014a) reported a median whole blood/plasma conversion factor of .68 with a range between individuals from .31 to 1.1, showing a poor relationship. Although the preponderance of research clearly shows whole blood to serum or plasma ratios are less than one, the large range in ratios also indicates poor ***reliability*** in the conversion factors between individuals. Plasma or serum levels should not be used to draw inferences of whole blood levels for THC for an individual. This poor conversion factor is a major limitation of numerous empirical studies, as serum/plasma cannot accurately be generalized to whole blood and vice versa for any individual. In fact, most of the studies of THC concentrations in blood are based in plasma, not whole blood. Yet, in North America, whole blood is required for most legal cases.

Despite the substantial degree of variability between individuals and over time for the same individuals, conversion factors from serum/plasma to whole blood are frequently cited. The most commonly cited conversion factor is .5 (1 ng/mL THC in whole blood is equivalent to 2 ng/mL in serum) reported by Grotenhermen et al. (2007). Couper and Logan (2004) report the average conversion of whole blood to serum/plasma for THC is .55 (or 1 ng/mL in whole blood, which is equivalent to 1.82 in serum or plasma). No empirical studies to support either of these conclusions were cited. For drawing a rough estimate of the average conversion for a **group**, a conversion rate of .5 is common; however, when it comes to an **individual**, this conversion is unacceptable because the variability of the ratio between people and for the same individual at different time points after use is substantial. Many studies used blood serum, which have higher THC concentrations than whole blood.

Detection period of THC in blood after smoked cannabis—Several research studies have examined the elimination and detection periods in blood, although many of these studies were based on blood serum or plasma rather than whole blood. In terms of elimination times after smoking cannabis, a controlled dosing study by Huestis et al. (1992) decades ago recorded blood plasma cannabinoid concentrations of THC, carboxy-THC and

hydroxy-THC at 34 different time points for six experienced users with high-dose (3.55% THC) and low-dose (1.75% THC) marijuana cigarettes. Peak concentration levels of THC were recorded under 15 minutes for every subject. Peak concentration levels of hydroxy-THC occurred at a longer time period (under 30 minutes), and peak concentration for carboxy-THC was longer than both at four hours or less. Detection periods for THC, the time periods from last use in which each compound can be detected, varied considerably between subjects. For example, one subject THC was last detected at three hours and for another subject 27 hours. Although THC levels declined over time for the group, individual readings could be erratic at different time points. For example, the THC concentration for one subject at six hours was zero and at 12 hours was 3.6 ng/mL. Detection periods were shortest for THC and longest for carboxy-THC. For hydroxy-THC, there generally was a delayed onset with a detection period in between THC and carboxy-THC. In a similar study of whole blood THC concentrations at different time points, Fabritius et al. (2013) reported averages slightly lower than those Huestis et al. (1992) but a similar pattern over time. The findings from the Huestis study have been replicated (Huestis & Cone, 2004).

In a study by Hunault et al. (2014), average THC serum blood concentrations after smoking cannabis were presented for 24 recreational users. Three different doses of cannabis were administered to participants. For each dose, THC blood levels increased rapidly within the first 15 to 30 minutes after smoking and declined about 90% to low levels within two hours, followed by a very gradual decline afterwards. In the high-potency condition (69.4 mg THC), THC concentration levels spiked at about 210 ng/mL in serum blood within the first half-hour, and in the low potency condition THC spiked at about 140 ng/mL. By four hours, THC levels declined to low levels (exact numbers were not provided in the report) and remained at low levels for the eight hours of the study.

In a controlled administration study by Spindle et al. (2019a) the detection times in whole blood were compared for smoked versus vaporized cannabis. They administered three doses of cannabis: a placebo, 10 mg and 25 mg THC. Average THC levels were higher for vapourized cannabis, based on exact measures at different time points. Peak blood THC levels were below 35 ng/mL in every case, and markedly lower than other studies, even when accounting possible differences due to the detection of THC in whole blood rather than serum.

A controlled dosing study (Meier et al., 2018) examined CBD and THC concentrations in blood serum from very-low-THC concentration marijuana (.8 and .94%)

for only two subjects. THC levels were above the ***limit of detection*** in the first hours for the chronic smoker and about 45 minutes for the naïve smoker. The spike in THC levels, like other studies, occurred at about 15 minutes, but THC levels were much lower (around 3-5 ng/mL) at these peaks, comparable to the study by Spindle et al. (2019a) but unlike other studies. Poor convergence between studies in THC blood concentrations suggests that the analytic process for detecting compounds may not been fully standardized.

In terms of smoked cannabis, detection periods for THC in blood can be extremely long among frequent users. In a study by Karschner et al. (2009), long-term heavy smokers of cannabis were monitored for seven days of abstinence in an in-patient setting. One daily user had a THC blood concentration level of 3.7 ng/mL six days after abstinence, a concentration level subject to penalties under Canadian law. Bergamaschi et al. (2013) found THC levels above .3 ng/mL 30 days after abstinence. A later study by Desrosiers et al. (2014a), concluded that 16.7% of frequent cannabis users had THC concentrations exceeding 5 ng/mL at 30 hours after use.

In a review paper by Peng et al. (2020) of residual blood THC levels in frequent cannabis users, the authors concluded that levels above 2 ng/mL do not necessarily reflect recent use. Three studies were found where subjects had THC concentrations above 2 ng/mL after six or more days after abstinence and two studies found levels above 5 ng/mL after one day. These findings mean that interpretation of blood for impairment in frequent users is highly problematic.

Detection period of THC in blood after ingested cannabis—THC blood concentration levels rise very little when orally ingested compared to when smoked but higher concentrations of a psychoactive metabolite of THC, hydroxy-THC, are found. More information on the differences of the compounds in blood for smoked versus ingested cannabis is described later in Chapter 4, where a study by (Ménétrey et al., 2005) is highlighted. In addition to the studies described below examined THC in blood from oral doses of cannabis.

Huestis et al. (2006) and Vandrey et al. (2017) conducted controlled cannabis administration studies with THC concentrations in either plasma or blood. Huestis et al. (2006) administered oral doses of cannabis to 18 subjects with histories of cannabis use and analysed 306 plasma specimens for THC and carboxy-THC. Only 90 specimens had THC and carboxy-THC concentrations above the ***Limit of Quantification*** at .5 ng/mL THC, indicating low detection thresholds of THC in blood. In a study by Vandrey et al. (2017) 18 occasional

users (no use in the prior three months) were administered 10, 25, and 50 mg THC doses in brownies and THC confirmatory tests (LC-MS-MS) in whole blood for exact THC concentrations at multiple time points from 28 minutes up to 126 hours after exposure. The THC blood concentrations were extremely low for all subjects. Eight of the 18 subjects never had THC concentrations exceeding 1 ng/mL THC at any time point. The highest concentration level was 5 ng/mL by only one subject. The highest concentrations were found at 1-4 hours after ingestion, with THC concentrations of 4 ng/mL in several subjects. THC was detectable in one subject 22 hours after use at 1 ng/mL. These studies illustrates that THC concentrations are extremely low in blood when cannabis is ingested.

Milman et al. (2011) gave subjects very large multiple doses of either 100 or 120 mg THC per day over eight days to experienced cannabis users. They reported concentration levels in blood plasma in microgram per litre (ug/L), which is equivalent to nanograms per millilitre (ng/mL). Concentration levels increased with additional doses, with median peak concentrations after the last dose of only 14.6 ug/L. Given the extremely large doses and repeated administrations, this median peak is very low compared with peaks found for smoked cannabis.

Newmeyer et al. (2017a) compared oral fluid detection times of THC comparing frequent and occasional smokers after an ingested cannabis dose. The average detection time was 39 hours in frequent users and only 23 hours in occasional users ($p<.003$), findings that were also found with blood tests. The longer detection time among frequent users is likely due to smoked versus ingested cannabis.

Several conclusions can be drawn from the studies in this section. The detection periods in blood are shortest for THC and longest for carboxy-THC (hydroxy-THC is in between the two). For smoked cannabis, THC levels spike within 15 minutes of use at high levels but peak THC blood concentrations are delayed and much lower when ingested. When smoked concentrations rapidly decline to a lower level that typically can be detected for several days after abstinence among daily users. Heavy daily users have longer detection periods than occasional users, due to build-up of THC in the blood over time. THC concentrations vary considerably at different time points for subjects administered the same amount of cannabis. Ingested cannabis produces much lower peak blood concentrations than smoked cannabis. Therefore, if the purpose of the test is to assess validity of the specimens in terms of impairment, cut-offs must be analysed separately for

smoked versus ingested cannabis. This fact can be problematic in real world situations where the method of cannabis consumption is unknown.

Oral fluid

In this section, I describe research on confirmatory oral fluid tests to detect THC from smoked and ingested cannabis. Confirmatory oral fluid (less technically called saliva) tests can be used to detect THC, the psychoactive ingredient in cannabis. Oral fluid have several practical advantages over blood or urine. In particular, oral fluid tests are less invasive, simpler to collect and touted as the best screening tool for law enforcement. A practical drawback of oral fluid tests is that some individuals have a dry mouth and are unable to provide a sufficient saliva sample for analysis (Owusu-Bemphah, 2014; Pil & Verstraete, 2008). Also, a variety of confirmatory testing methods exist and a concern is the degree to which the analytic approaches are comparable and standardized (Sobolesky, 2018). A major issue with respect to oral fluid tests is whether they can be validity used to detect those who are impaired. In this respect, the mechanism by which they detect THC is important. It was commonly thought that THC can be detected in two different ways after cannabis use: (1) directly from residuals and (2) indirectly from the bloodstream in the oral cavity. Drummer (2006) claims "there is significant local absorption of the drug in the oral cavity which increases the concentrations for a period after use of drug." Research shows carboxy-THC (THCCOOH), which is created through metabolism of THC, can also be detected in oral fluids, and has been cited to suggest that THC found in the oral cavity provides evidence of active smoking rather than direct residues left behind after smoking (Milman et al., 2012). Lee and Huestis (2014) claim blood to oral fluid transfer is minor. The research studies conducted suggests these two mechanisms of detecting THC in oral fluids may only valid when cannabis is smoked, as some experts in studies reviewed below, suggest when cannabis is ingested, oral fluids only pick up direct remnants of THC in the mouth.

Oral fluids are not suitable for detecting impairment due to contamination from remnants in the mouth. Tests positive for THC from traces left in the mouth, does not mean THC is in the blood or affecting behaviour (Karschner et al., 2020). In a study by Langel et al. (2014) with paired oral fluid and blood tests, numerous subjects had positive or high THC readings over 200 ng/mL in oral fluid but non-detectable amounts of THC in blood, possibly due to oral contamination.

Brushing ones teeth or rinsing ones mouth after use can greatly reduce THC concentration levels in the mouth. In an empirical study by de Castro et al. (2014), 11

subjects, who smoked an average of 32 joints per week, smoked their usual doses and oral fluid tests were taken at various time points after rinsing with mouthwash, whole milk or Kleaner (a product advertised to avoid OF positive tests for cannabis) and water. On day three scenario, oral fluid tests were taken both before and after a water rinse. This scenario allowed for a best analysis of the influence of rinsing the mouth on OF results. Statistically significant reductions in oral fluid THC concentrations were found from before to after a water rinse. Four of 11 subjects had THC concentration levels below 10 ng/mL at three hours. The rinse appeared to have a greater effect shortly after use. At 12 hours after smoking, the average THC concentration without a rinse was 10.8 (SD=7.0) whereas with a water rinse the average THC level was 7.6 (SD=5.5).

Detection period of smoked cannabis in oral fluids—In a study by Lee et al. (2012), 10 cannabis smokers each smoked a 6.8% cannabis cigarette weighing .79 g. The dataset for this study appears to be the same dataset as reported by Milman et al. (2012). Inclusion criteria included specific blood pressure and heart rate readings. Oral fluid THC levels were typically above 300 ng/mL in the first 15 minutes and over 100 ng/mL within the first hour after use, with a massive range in peak levels found between 68 and 10,284 ng/mL. All subjects had positive THC readings from oral fluid tests six hours after use, with a range of between 2.1 and 44.4 ng/mL. This study found substantial variations in THC levels between subjects for the same time points after smoking. Similar results were found in other studies, as described below.

A similar study by Milman et al. (2012) reported oral fluid THC concentration readings at different time points for 10 individuals administered a 6.8% THC cigarette. At .5 hours, four of 10 subjects were unable to provide a sufficient sample due to a dry mouth. At one hour, THC levels ranged between 35 and 1030 ng/mL—a massive degree of variability between individuals. At two hours, the median THC level was 31.7 ng/mL, with a large range between 11.6 and 1310 ng/mL. At four hours, when subjects would not be expected to be under the influence of cannabis, the median was 8.3 ng/mL with a range from 2.1 to 245 ng/mL. Four of six subjects had positive readings above the limit of quantification at 22 hours after use and one subject has a reading of 10.3 ng/mL. Clearly, the variability between subjects administered the same amount of cannabis is extremely high.

Toennes et al. (2010) administered doses of smoked cannabis in doses from 22 to 47 mg THC, intended to provide 500 ng THC per kg of body weight among 10 occasional and

10 chronic users, an unusual procedure, an atypical approach in controlled dosing studies. Although Toennes et al. (2010) reported oral fluid in grams rather than millilitres, they are equivalent with 992 mg equal to one mL (Kauert et al., 2006). Chronic users had much higher THC peak concentration levels at both one and eight hours. Again, the variability between subjects in concentration levels was enormous at each time point. At one hour, THC levels ranged between 49 and 794 ng/mL in occasional users and between 24 and 1436 ng/mL in chronic users. The authors found that THC concentration averaged 8 ng/mL at eight hours post-dose for occasional users and 16 ng/mL for chronic users. In addition, the authors reported a standard deviation of 7.4 for occasional users and 14.5 for chronic users at eight hours, which indicates very high variability among subjects. This study found four of 11 occasional users and six of 11 chronic users had readings over 10 ng/mL at eight hours. The authors also compared oral fluid and serum readings in a series of samples. They found that 24.1% of the negative serum samples tested positive when oral fluid samples were analysed. As found in other studies, the oral fluids to serum ratios were highly variable, with variations of ratios from .3 to 425 ng/mL. The authors concluded: "The large inter- and intra-individual variability observed precludes a reliable estimation of THC serum concentrations from oral fluid data…" (Toennes et al., 2010; p. 216).

In a study by Niedbala et al. (2001), two specimen of oral fluids (left and right side) were tested with both immunoassay and confirmatory methods at time points up to 72 hours after use. Cannabis was administered in three ways: smoked, passively (second hand smoke) and ingested by marijuana-laced brownies. Findings from smoked and passive cannabis are presented here. Generally, those with THC concentrations above .5 ng/mL from a confirmatory test also tested positive with the immunoassay. Findings were similar to Milman's study (2012) in terms of THC concentrations at different time points for smoked cannabis. Only one of 20 readings for the 10 subjects who smoked cannabis tested positive for THC concentrations at or below 2 ng/mL at 24 hours. Finally, passive exposure did not trigger either confirmatory oral or urine positive tests.

Also, Fabritius et al (2013) also conducted a controlled dosing study of THC concentration levels after smoking for both occasional and heavy users. The figure for heavy users is poorly presented; however, an overall conclusion is that concentration levels over time are similar to other studies. Anizan et al. (2013) found THC positive oral fluid tests for all (n=14) subjects 13.5 hours after smoking cannabis and 64% were positive at 30 hours. Another study focused on detection times for THC in oral fluids (.3 ng/mL threshold) among

frequent users (Andås et al., 2014). They found that negative samples could test positive at subsequent time points and that positive samples could be detected eight days after abstinence in one subject. Since the detection of THC was the main focus of this study, the findings are not useful for determining a possible cut-off for impairment. Newmeyer et al. (2014) studied detection of various compounds in a controlled dosing study of frequent and occasional smokers. They noted THC had the widest detection window among the compounds investigated.

Like blood tests for THC, frequency of cannabis use appears to be highly related to the detection periods and concentration levels at different points in time from oral fluids. Verstraete (2004) conducted a review of the literature on detection times of drugs in blood, oral fluids and urine. They concluded the typical detection time for cannabis in oral fluids is about 34 hours. Later, Dyer and Wilkinson (2008) distinguished between single-use and chronic users, and provided approximate detection times of 4-14 hours for single-use and 4-30 hours for chronic heavy use. More recently, Lee et al. (2011) reported positive oral fluid tests of THC for 48 hours after abstinence among daily cannabis smokers, substantially longer than the detection periods noted in the reviews by Verstraete (2004) and Dyer & Wilkinson (2008). For smoked cannabis, oral fluid tests appear to detect both diffusion of THC from blood to oral fluids, and direct remnants of THC Drummer (2006).

Overall, it can be summarized from studies in this section that high average levels of THC are found in the first hour after smoking, followed by a gradual decline at subsequent time points. Extremely large variations between subjects in THC levels were observed in every study. Although confirmatory tests have been proposed by some as good biomarkers of impairment, persuasive research does not exist to show this is feasible with reasonable accuracy based on the number of factors influencing detection periods. The aforementioned descriptions only referred to situations where cannabis is smoked. I found three research studies, described below, on detection of THC oral fluid when cannabis is ingested, and the findings are markedly different.

Detection periods of ingested cannabis in oral fluids—When cannabis is ingested, close to 100% of the THC detected are remnants. A study by Milman et al. (2011) of 10 daily smokers of cannabis involved subjects ingesting Dronabinol (synthetic THC) in the form of Marinol in 20-mg capsules for total doses of 40–120 mg/day with increasing frequency (every 4–8 hours around the clock). Although some positive confirmatory THC concentrations were found among these users shortly after admission, when subjects were

given high doses of THC in pill form, THC concentrations in oral fluids dropped dramatically but THC readings in blood plasma increased. Milman et al. (2011) described the THC concentration levels in oral fluid as due to smoked cannabis before admission, not ingested cannabis after admission. The average oral fluid THC concentration was below 2 ng/mL for six tests shortly after the first THC administration. As well, after three days, when subjects were given 120 mg/day, the detection rate of THC in oral fluid was only 3%, based on GC/MS tests. Based on the doses ingested, these subjects would most likely be impaired.

In a study described above by Vandrey et al. (2017) of blood tests, oral fluid tests were also administered to subjects who ate various doses of THC-laced brownies. Unlike the study by Milman et al. (2011), subjects generally tested positive (i.e. THC in oral fluid at or over 2 ng/mL) for tests within the first hour and were mostly negative at four hours. Most subjects were negative after six hours, although one subject had a positive reading at 2 ng/mL at 22 hours. Some subjects had negative readings at one point in time and positive readings at a later point in time. The authors' interpretation was that the positive readings appear to reflect local topical residue rather than due to ingestion of the drug (Vandrey et al., 2017; p 83).

In a study cited earlier by Niedbala et al. (2001), three subjects (a very small sample) were administered THC-laced brownies and confirmatory oral fluid tests conducted. The detection period in oral fluids also was four hours for two subjects and 72 hours for one subject.

A conclusion from the controlled-dosing studies on ingested cannabis is that oral fluid tests are inaccurate for detecting impairment. Oral fluid tests appear to only detect residues in the mouth, which do not necessarily mean impairment. Based on the study by de Castro et al. (2014), if subjects rinse their mouths after use, their THC concentration levels would be greatly reduced. As well, positive tests can occur with brownies shortly after use due to residues, but if THC is ingested in pill form it appears no residue is left and oral fluid tests are unable to pick up use in this situation. These latter cases would be false negatives if the purpose is to detect impairment or use. In summary, oral fluid has poor validity for ingested cannabis and is dependent on direct residues for THC detection. This means that among those actually impaired from ingested THC in pill form, 100% will be false negatives (i.e. impaired but not detected by the tests) regardless of the cut-off.

Oral fluid tests are better for the detection of smoked cannabis than ingested cannabis. Unlike research that indicates THC from smoked cannabis can be detected by

absorption in the oral cavity, research for ingested cannabis suggests this absorption does not occur. The detection period for smoked cannabis has been reported to be quite long at approximately 34 hours compared with ingested cannabis. For ingested cannabis, the detection period was approximately four hours when cannabis was eaten in the form of brownies based on one study (Vandrey et al., 2017), but more research is needed. Although higher cut-offs shorten the detection period, no study has been conducted that provides a compelling case that a higher cut-off can be validly used to detect impairment from smoked cannabis.

Correlations between blood and oral fluid THC—In addition to the controlled-dosing studies above, studies of paired oral fluid and blood samples from different subjects have been conducted to assess the strength of correlations between the two. In the cited studies below, multiple observations of the same subjects were not taken, therefore meeting the assumptions of the statistical tests. Three studies were found that met the inclusion criteria: Gjerde and Verstraete (2011), Langel et al. (2014) and Vindenes et al. (2012). These studies were conducted with sample sizes between 100 and 4,080 participants, and had very low coefficients of determination (r^2) of .12, .21 and .030, respectively. These findings demonstrate that oral fluid tests of THC are not closely related to blood and therefore are not a good substitute for blood tests. Additionally, when cannabis is ingested, the relationship between THC in blood and oral fluids is particularly poor and has been shown to be poor in controlled dosing studies. For example, Newmeyer et al. (2017a) conducted a study of oral fluid and blood concentrations from cannabis brownies and concluded: “A reliable conversion between blood and OF THC concentrations does not exist” (p.660). An explanation for why oral fluid tests lack validity for smoked cannabis is because they detect two phenomena – direct residues from smoking cannabis and THC diffused into the oral cavity. For ingested cannabis, only direct residues can be detected, which are not closely related to the amount of THC in the blood. Whether cannabis is smoked or ingested, the THC detected is not a direct measure of how cannabis is affecting the person.

As mentioned previously, oral fluid tests are much more practical than blood tests to administer in a roadside situation and therefore they have received considerable interest in demonstrating their validity through comparisons to blood tests. In one paper, this desire to demonstrate validity has culminated in a violation of the purpose of statistics. Gjerde and Verstraete (2011), created a statistical procedure, “prevalence regression,” where

percentiles between THC in oral fluids and blood were plotted and a new regression analysis was conducted with only nine data points. The r^2 value increased from .21 to .99, giving an illusion of a strong relationship. Essentially this method uses measures of central tendency (percentiles) that mask the reality of substantial variability between subjects in terms of oral fluid and blood ratios. In fact, if one uses this approach to create only two data points instead of nine, virtually any scatter plot of data, no matter how poor, can be turned into a perfect linear relationship (r^2 =1.0). No reference from a statistical expert was provided by the authors to support this approach. The authors did acknowledge large variations in oral fluid and blood ratios for THC and they should have just plotted the curve of best fit using basic regression methods. In summary, this statistical procedure of prevalence regression defeats the purpose of regression analysis as it essentially eliminates the variability between subjects, an important consideration for validity.

THC concentrations in oral fluid are much higher than in blood. The average conversion factor can be roughly estimated even with poor correlations. From the published studies, I estimate an average oral fluid/whole blood ratio between 20 and 60, with higher ratios noted shortly after use (Hartman et al., 2015a; Langel et al., 2014; Vindenes et al., 2012).

Some authors have speculated that oral fluid samples can be analysed with gold standard confirmatory methods to draw conclusions of impairment. To date, use of oral fluids for this purpose is not supportable by existing science. An important finding of the controlled dosing studies cited is massive variations in THC concentration levels both between subjects and within subjects administered the same amounts of cannabis and the different detection periods for smoked and ingested cannabis.

Point of collection for oral fluid tests—Since experts agree blood is the best biological sample for assessing impairment, if oral fluids are to be used as a substitute of blood for this purpose, one would expect a strong relationship between them. A major hurdle of testing in field situations is the development of a rapid, portable device that also can **accurately** measure the level of different drug compounds in the body. This task is not feasible with current confirmatory methods with any type of biological sample. A particular type of immunoassay screening test for drugs is the ***point-of-collection*** test*,* a drug test that produces findings within 10 minutes. The test detects numerous cannabinoids that are closely related based on their molecular structure and is therefore used as a screening test for cannabis. There are about a dozen point-of-collection tests on the market for either

urine or oral fluid samples, though research show these tests vary considerably in terms of validity (Blencowe et al., 2011; Cone, 2001; Drummer, 2006; Ginsburg, 2019). In a recent study, Ginsburg (2019) reported the validity of the point-of-collection tests from oral fluids compared against confirmatory methods. The accuracy of these devices varied considerably, with sensitivities from 0 to 92.3% and specificities from 15.4% to 100%, depending on the device.

In a study on oral fluid point of collection for possible use in Canada, tests for cannabis (and other drugs) were validated against confirmatory tests of known drug users who acknowledged drug use in the previous three hours and known negative samples from police officers (Beirness & Smith, 2017). The accuracy of the point-of-collection tests was good at 92.3%, sensitivity (86.9%) and specificity (95.5%). An assessment of whether those with positive tests are impaired was outside the scope of this study.

In Canada, the Dräger DrugTest 5000 has been selected as the point of collection screening device for law enforcement use. The manufacturer describes this test as fast and accurate. The validity of the oral fluid Dräger DrugTest 5000 was assessed against THC confirmatory tests with oral fluid and blood, based on ingested cannabis-laced brownies (Newmeyer et al., 2017a). The authors indicate this is the first study to assess this device using cannabis edibles, an important area of inquiry, considering consumers' increasing interest in edibles. Sensitivity and specificity were good (i.e. over 90%) against the oral fluid confirmation test but only when the confirmatory test was above 5 ng/mL THC. THC concentrations became undetectable in occasional users 12 hours after use but lasted much longer for frequent users. THC concentration levels in blood peaked much later than oral fluids. They concluded that positive oral fluid concentrations were primarily due to direct contamination from the brownies. More research is needed on oral fluid concentration levels after cannabis use.

The Dräger DrugTest 5000 and another point-of-collection test were originally proposed by the Canadian government to screen drivers for cannabis. They were field-tested with police officers (Keeping & Huggins, undated). Police described over 90% of tests as easy or very easy to administer, yet other findings from this study are disturbing, suggesting use in the field may be fraught with limitations. Specifically, (1) 65% of tests were administered outside the manufacturer's suggested operating temperatures, (2) three devices were found by police as defective, giving only positive results, and (3) officers had difficulty administering a swab for approximately 40% of the tests (Keeping & Huggins,

undated). Clearly, potential pitfalls of using oral fluid tests in real-world Canadian conditions were identified by this study. The proposed implementation by the Canadian government of the Dräger DrugTest 5000 despite these limitations illustrates little concern for both the feasibility and accuracy of the device in real life situations.

When reviewing empirical research, it is important to keep in mind the purpose of the studies. If the purpose of the study is to detect prior drug use rather than impairment, some point-of-collection oral fluid tests have good validity when cannabis is smoked; however, little is known about the accuracy of these tests for ingested cannabis. Most studies focused on comparison of oral fluid tests with confirmatory tests for the purpose of detecting use, and do not speak to the issue of performance deficits or impairment. Hence, we are still left with a poor understanding of the relationship between oral cut-off levels and cannabis impairment.

Urine

Urine tests, unlike blood and oral fluid tests, can be tampered with to give a false reading. Tampering is usually done with the intent of producing a false negative. A wide range of commercial products and adulterants exist that have been reported to produce false negatives (i.e. hide what would otherwise be a positive test). Jaffee et al. (2007) identified 12 commercial products that have been found to successfully mask marijuana, amphetamines, opioids, and cocaine or its metabolites. Simple household adulterants, such as bleach, vinegar, Drano, and detergents have been shown to be effective for producing false negatives. Although users getting tested generally aim for false negatives, some products, such as ibuprofen and baby wash soap have been reported to cause false positives (Kapur & Aleska, 2020). To address the possibility of mistakes, urine samples are typically first analysed to ensure the sample has not been adulterated.

Two common approaches to create false negatives are dilution and substitution with clean urine. Drinking large quantities of water can cause dilute urine and lower THC concentrations of THC. Dilution can be detected with creatinine checks. Another method of foiling the test is urine substitution from clean donors. This can involve elaborate prosthetic devices and warming mechanisms to evade detection. To counter this deception, direct observation of urination and testing samples for temperature, creatinine, specific gravity, pH, and oxidizing adulterants are recommended (Jaffee et al., 2007).

Detection period of cannabis in urine—Urine tests are not good specimens for identifying cannabis impairment. The detection periods for different compounds are much

longer than for blood and oral fluids. As well, carboxy-THC is typically tested in urine, a metabolite of THC that is not psychoactive. Urine tests are not suitable for detecting when a substance was used, primarily due to the long detection window, which can be up to 60 days for heavy users (Verstraete, 2004). For occasional users, the detection period is typically within 3-4 days. As well, this window of detection for cannabis is highly variable and may be affected by numerous factors, including time and size of last dose, single-dose versus multiple doses, volume of fluid intake prior to collection, kidney function (excretion of drug), liver function (metabolism of drug), as well as the kinetics of drug distribution, including volume of distribution and body fat. That being said, they are not feasible to assess impairment (Kapur & Aleska, 2020). In addition to the long detection window, carboxy-THC is first detectable in urine two to six hours after use (Swotinsky, 2015; p. 216) and therefore, those testing negative could be impaired if they used within a few hours before the test.

In a study by Brenneisen et al. (2010), 12 male volunteers were administered a marijuana cigarette, then urine tests for different cannabinoid compounds were taken at various time intervals. Not a single subject had a reading above 15 ng/mL of carboxy-THC (a typical cut-off for workplace drug testing) within a four-hour period of smoking. The authors note that urine has a wide detection window that "does not allow a conclusion to be drawn regarding the time of consumption or the impact on the physical performance" (Brenneisen et al., 2010; p. 2493). Most cannabinoid compounds are detectable for very long periods after use. If the confirmation cut-off for carboxy-THC is 15 ng/mL, a threshold adopted by most workplace drug testing programs, it is unlikely an individual who used within a four-hour window would even test positive.

Little is known on the degree to which the detection period for carboxy-THC varies, depending on whether cannabis is smoked or ingested. A study by Niedbala et al. (2001) three subjects were given brownies with THC and positive confirmatory urine tests over 15 ng/mL were found at 72 hours. These subjects had a history of recent cannabis use, which also could explain the positive findings.

In addition to carboxy-THC, both hydroxy-THC and THC can be found in urine samples, though these latter two compounds have been infrequently tested with urine. In a study by Brenneisen et al. (2010), THC was detected in urine for all subjects at two hours, and one subject's at eight hours post-use. Urine samples to detect THC have a much shorter detection window than carboxy-THC. THC can be detected between two and eight hours after use, depending on the ng/mL cut-off. More research on detection of THC in urine,

especially with daily and heavy users and ingested use is needed. Hydroxy-THC usually peaks between two and six hours after use. Overall, urine can be ruled out as a viable sample to assess performance deficits, regardless of the compound being detected. It will produce false negatives within the two-hour period after use in occasional users.

Breath

Breath tests can be used to detect the presence of several drugs from exhaled air (Ossola, 2015). However, because the concentration levels of exhaled air are extremely low, the compounds can only be detected by mass spectrometry equipment. This equipment requires large amounts of space (similar to computers in the 1970s), which makes them highly unsuitable for field use.

Breath detection research is currently being conducted by companies such as Cannabix and Hound Labs to develop a breath test for THC compounds. Cannabix is working on a portable device using an ion spectrometry analysis. The first published article indicates the device targets recent use within a three-hour window and correlates well with THC levels in blood (Lynch et al., 2019). A portable test that could detect recent use within a three-hour window after last use could be useful for traffic safety. It is unlikely the device will be effective for ingested cannabis, unless it can also detect hydroxy-THC (described in more detail in this book).

Summary of detection periods for urine, oral fluids and blood— **Table 6** below provides a summary of the approximate detection periods for cannabis in urine, oral fluids and blood. Columns 2 through 4 show the detection periods of cannabis for drug tests from urine, oral fluids and blood. As previously mentioned, detection times can vary depending on a variety of factors. Overall, the detection period for cannabis is shortest for blood and longest for urine tests. In Chapter 5, the duration times of the acute effects of cannabis will be examined. These times can be compared to the detection periods to speculate on how well each type of test can be used to detect cannabis impairment.

Table 6: *Typical detection times (or ranges) for drug tests with different specimens, based on common laboratory cut-off values*

Consumption method	Approximate detection periods		
	Urine	**Oral fluids**	**Blood**
Smoked	Depends on frequency of use Single use: 3 - 4 days[2,3] Moderate use: 5-7 days[2,3] Daily use: 10-15 days[2,3] Long-term Heavy use: >30 days[2,3]	48 hrs [1] Heavy use – unknown	Occasional users about 38 hrs[6] Frequent users – at least 7 days[7]
Ingested	No studies found	0 hrs if no residue is present[4], 22 hrs for direct remnants of THC[5]	Occasional users about 26 hrs[6] Frequent users – At least 48 hrs but could be due to prior smoking [6]

References: 1. Lee et al, 2011; 2. Moeller, et al., 2008; 3. Standridge et al., 2010; 4. Milman et al., 2010, 5. Vandrey et al., (2017) 6. Newmeyer et al., 2017a 7. Karschner et al., 2009

CONCLUSION

Currently, the more accurate methods to assess cannabis impairment are with confirmatory analytic methods to detect THC. Although some researchers have sought to detect multiple compounds or metabolites, none of this research has proven to be more accurate than THC detection alone to detect impairment. The important question is this: what cut-off should be used to best identify those who are impaired?

Comparisons can be drawn between the Breathalyzer for alcohol and blood tests for THC, which are summarized in **Table 7**. Blood is the gold standard for the purpose of assessing impairment from alcohol or cannabis. Breathalyzer tests for alcohol are an excellent substitute for blood tests and provide a close approximation of BACs. For THC

levels, confirmatory tests between blood and all other types of biological are poorly correlated and cannot be substituted for blood tests. Confirmatory drug tests have excellent validity for detecting specific cannabinoid compounds, whereas screening tests are poorer in accuracy.

The Breathalyzer for alcohol has numerous advantages over blood tests for THC, as the Breathalyzer is less invasive, requires little training to administer and offers quicker results. Clearly, the Breathalyzer has many advantages over blood tests when considering practical issues of implementation in the field.

For cannabis, THC, the main psychoactive compound, has been the most thoroughly researched biomarker of impairment. Hydroxy-THC is a metabolite which produces stronger psychoactive effects, but has not been well studied. Carboxy-THC is readily detected in urine and blood, but again, is not a viable biomarker for impairment due to its excessively long detection period. Generally, these compounds are detectable within different time periods after use, with the longest detection period for urine and the shortest detection period for blood tests. Future studies of THC in blood should report only whole blood concentration levels because conversion levels between whole blood and serum/plasma are unreliable.

Both blood and oral fluid tests can detect THC rather than metabolites such as carboxy-THC. Blood tests for THC have the shortest detection window and the best validity for impairment. Blood is still not suitable for assessing the psychoactive effects on users, but better than oral fluids, urine or other biological samples. Oral fluids and urine have longer detection periods than blood. An additional complication, especially with blood and oral fluid analyses, is how cannabis was consumed. THC blood levels are much higher when smoked compared to when ingested, making conclusions of psychoactive effects challenging. If very high concentration levels (i.e. > 20 ng/mL) are found in whole blood, there is a good chance cannabis was smoked, not ingested, and used within the hour. There is strong evidence that when ingested, oral fluid tests can only detect direct contamination in the mouth from cannabis. This means that if THC is taken in pill form, oral fluid confirmatory tests for THC will be negative. Since the detection periods are very different for smoked and ingested cannabis, oral fluid tests are not suitable for determining impairment.

Table 7: *Comparison between the Breathalyzer for alcohol and blood tests for THC*

	Breathalyzer (Alcohol)	Blood test (THC)
Accuracy compared with other biological samples	• The Breathalyzer is an accurate substitute for a blood test to detect BAC. • Breathalyzers tests are excellent—r^2 > .8 for correlations of BAC by blood and breath (Zuba, 2008). • Oral fluid tests are also a good alternative to blood tests • Urine is not a suitable alternative to blood.	• Only blood tests are sufficiently accurate to detect THC concentration levels. • Oral fluids have a poor linear correlation with blood—r^2 values range from 3% to 12% of THC concentration in blood and oral fluids. Confirmatory oral fluid tests only detect direct residues in the mouth when cannabis is ingested. • Urine is not a viable alternative to blood tests.
Practicality	• Non-invasive. • Requires little training. • Provides quick results.	• Invasive. • Requires training. • Requires laboratory methods with GC/MS for confirmatory tests.

Blood test findings are frequently reported in the research literature in terms of serum, or plasma; however, for legal cases, whole blood is typically required, making generalizations from research to legal situations problematic. Although some researchers have recommended simple conversion ratios of THC serum/plasma-to-whole blood, research shows this ratio is too variable between people to adopt a specific conversion ratio. THC concentration levels in serum and plasma are roughly equivalent.

In this Chapter, I examined different detection approaches for alcohol and cannabis. In the next Chapter, I examine the pharmacokinetics of alcohol and cannabis.

CHAPTER 4

Pharmacokinetics of alcohol and cannabis

PHARMACOKINETICS

Pharmacokinetics is a branch of pharmacology that focuses on the movement of drugs within the body and involves issues of absorption, distribution and elimination of drugs in the human body. These three factors are related to the detection of a drug. This discipline is particularly useful for understanding the time course of drug concentrations in the blood after use, and for understanding the mechanisms for performance deficits. With this information, thresholds can be chosen to roughly map drug concentrations onto typical periods of being under the influence. These issues are best understood through controlled dosing studies. For a more technical and in-depth discussion of pharmacokinetics of cannabis, see Grotenhermen (2003) and Pertwee (2005).

Solubility

A major factor that influences absorption, distribution and elimination of substances and the choice of the best biological specimen is the properties of the substances themselves. Solubility refers to the ability of a substance to dissolve in a given solution. Solubility affects absorption and elimination rates in addition to determining which body compartments a substance will be distributed to. An important factor to consider is whether a substance is water soluble or fat soluble. Concentration levels in blood of water-soluble substances (i.e.

alcohol) correlate more closely with concentration levels found in the brain. On the other hand, fat-soluble substances such as THC have quite different concentration levels in the brain than in the blood. Collection of direct samples of brain tissue may be the most accurate way to detect impairment from biological samples but is not feasible in living persons, thus the best alternative of a biological specimen for chemical detection is blood.

Alcohol—Alcohol is water soluble, and as such, it is fairly evenly distributed in the blood, brain and other organs. This means that blood is a good indicator of the action of alcohol on the brain.

Cannabis—The main psychoactive component of cannabis is delta-9-tetrahydrocannabinol (THC). About 100 closely structurally related compounds to THC (***cannabinoids***) and over 500 other chemicals have been discovered in cannabis (Huestis & Smith, 2018). THC is a fat-soluble molecule that preferentially distributes to fatty tissues and fatty organs, such as the brain and liver. High-perfusion tissues, including the liver, will absorb THC at a much quicker rate (Ashton, 2001). THC is then released back into the blood at a lower and largely unknown rate**.** THC will also be slowly distributed to and redistributed from low-perfusion tissues like skeletal muscle.

Absorption and distribution

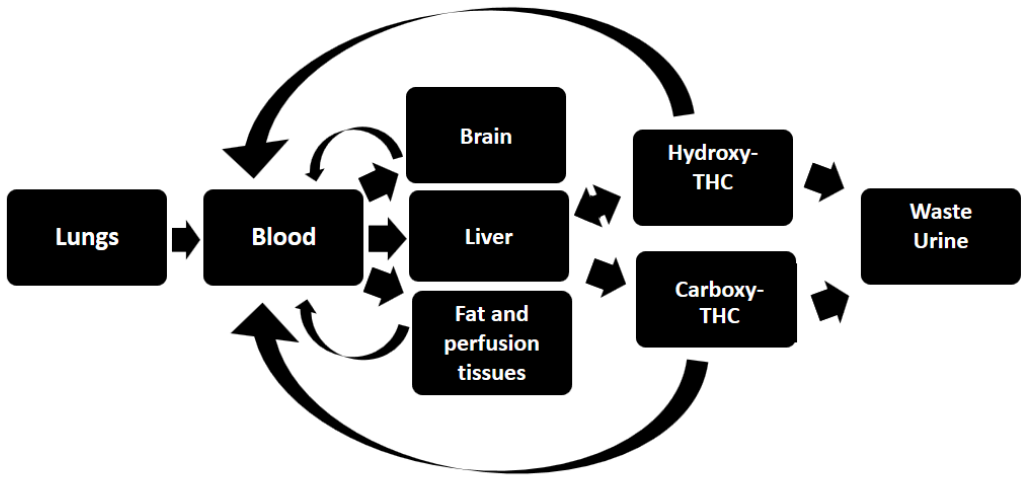
Absorption refers to how quickly a substance is absorbed into the body and distribution refers to how substances migrate to different body parts and into cells or across tissues and organs, and in particular the brain. Biological tests for alcohol and cannabis are indirect measures of the influence they have on the brain, and, as mentioned above, direct tests of the brain are not feasible. These indirect measures are associated with errors due to various factors. One influential factor is how drugs are consumed: whether they are taken orally, intravenously or inhaled.

Alcohol—Alcohol, which is only ingested orally, is quickly absorbed from the stomach into the blood. It reaches ***equilibrium*** between the blood and brain compartments in the first half-hour after drinking and remains fairly constant thereafter.

Smoking cannabis—After smoking cannabis, THC is rapidly distributed from the lungs to blood (see **Figure 1**). It then travels to the brain, fat and perfusion tissues, as well as the liver. The liver produces two main metabolites (by-products of the metabolism): first is hydroxy-THC, a psychoactive substance, and second is carboxy-THC, a non-psychoactive

substance. The majority of these metabolites are excreted in urine along with small amounts of THC (Brenneisen, 2010). What remains is redistributed in the bloodstream. THC levels rise very rapidly in blood after smoking, demonstrating rapid absorption, peaking within three to 10 minutes (Grotenhermen, 2003; Hunault et al., 2014). In one study, the range in the peak amount of THC in the high dose condition was between 76 – 262 ng/mL in plasma (Huestis et al., 1992), demonstrating a great deal of variability between people. When cannabis is smoked, hydroxy-THC peaks later in the blood at concentration levels of about 3–15% of THC levels. The degree to which hydroxy-THC or the interaction of THC with hydroxy-THC creates additional performance deficits is unknown. Smoked THC is first absorbed in the blood and then quickly goes to the brain. Afterwards, THC peaks in high and low perfusion tissues and finally much is stored in body fat (Nahas, 1975). THC absorption and distribution after smoking cannabis are dramatically different from ingestion (i.e. eating it).

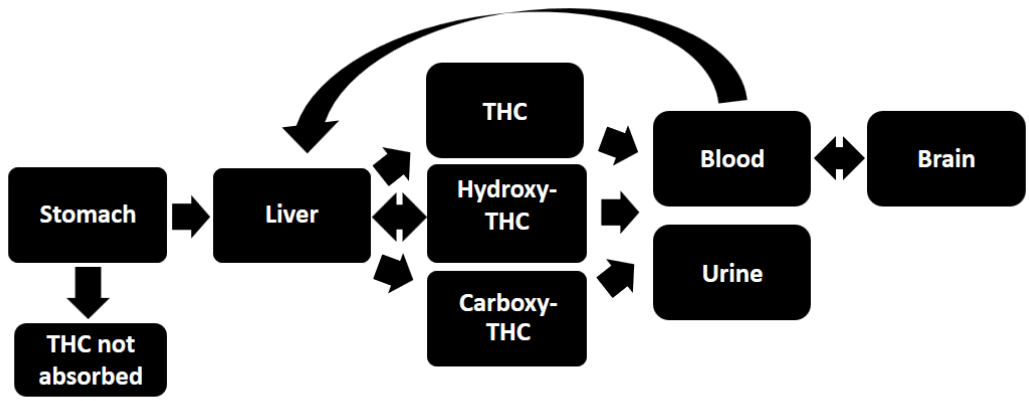
Figure 1: *THC distribution in humans from smoking cannabis*



Ingesting cannabis—When eaten, absorption of cannabis is much slower than after smoking (Kapur, 2009; Sharma et al., 2012), and distribution is much different, as cannabis is first absorbed by the stomach rather than the lungs (see **Figure 2**). This fact is particularly important, considering the emergence of a variety of edible products (Spindle et al., 2019b;

Swortwood et al., 2016). After it enters the stomach and blood, most of the drug then passes through the liver where it is metabolized and some THC passes into the blood, where it is distributed to other body parts including the brain. THC rapidly penetrates fat tissues where it is slowly redistributed back into the blood. Some of the THC is not absorbed and much of it is metabolized first into hydroxy-THC and second into carboxy-THC. Maximum THC levels are typically reached between the first and second hours, and it is possible that multiple peaks can be reached for some people (Sharma et al., 2012). These compounds then are distributed to the blood and brain. Peak THC concentration levels are typically low compared to smoking—about 5 to 10% of the peak level when smoked. However, levels of hydroxy-THC are much higher when eaten than smoked, often exceeding THC concentration levels (Ménétrey et al., 2005). The ratio of THC to hydroxy-THC is much greater when cannabis is smoked versus ingested. We do know that hydroxy-THC is psychoactive and several authors have suggested the high from ingested cannabis is more relate to hydroxy-THC than THC itself. More research is needed to understand the pharmacokinetics of ingested cannabis.

Figure 2: *THC distribution in humans from ingesting cannabis*



Elimination

Elimination is any process by which a drug is excreted from the body. This process is related to metabolism, mainly in the liver, and detection of drug concentrations. Individual differences in physiological characteristics, diet and food intake affect both absorption and elimination. As previously noted, fat-solubility strongly affects elimination; fat-soluble drugs can remain in the body for days, whereas water-soluble drugs are eliminated quickly and at a more consistent rate.

Alcohol—Several variables can affect the rate at which alcohol is eliminated from the body. Erik Widmark, a Swedish pioneer in the pharmacokinetics of ethanol (absolute alcohol) in the 1920s, first developed a method for measuring alcohol in the blood (Lerner, 2012). Although any given person metabolizes alcohol at a fairly constant rate, the elimination rate between individuals varies based on individual characteristics. Men generally metabolize alcohol faster than women and younger people sooner than older people. Elimination rates are higher among heavier drinkers and lower among lighter drinkers (Kapur, 2009). Wigmore (2014) and Zakhari (2006) reported that alcohol elimination rates vary approximately three-fold among individuals. Widmark also noted that eating food when drinking considerably lowered BAC level. Although alcohol elimination does vary among individuals, the more important issue is the degree of variation in performance between subjects at the same BAC. Early studies have found that performance at the same BAC level is worse when BACs are trending upwards rather than downwards (Jones & Vega, 1972). Extensive research shows that ***back-extrapolation*** of current BAC and a few key variables produces good estimates drawn on the amount of alcohol in a person at an earlier point in time.

Considerable research has been conducted to assess the potential degree of error for calculating the amount of alcohol in a person based on BAC and other measurements. Searle (2015) identified six potential sources of error and noted that the amount of error in estimates should be calculated on a case-by-case basis. Coefficients of variation (CV), a formula for expressing variation in samples that is useful for comparing measures with different units of analysis (explained more fully in Chapter 3), has been estimated by several authors. CV values below 15% for estimations of drink volume based on BAC and other individual factors indicate a high degree of accuracy. Breathalyzers in North America are calibrated to produce lower BACs in order to compensate for these errors.

Numerous BAC calculators available on the internet provide estimates of BAC. One produced by the American Addictions Centers includes five variables: sex, country (definitions of standard drinks vary among countries), weight, hours since having the first drink and number of standard drinks. I used this program to estimate the rate of absorption and elimination of alcohol for a 170-pound Canadian male consuming five drinks within one hour after the first drink. The approximate BAC level at different time points is plotted in **Figure 3** (below), along with similar data for THC concentrations in blood. This figure shows that a person drinking this amount of alcohol will have a BAC of about .06% alcohol after four hours. The rate of elimination is constant and it would take a full eight hours to obtain a BAC level of zero. Overall, we have a good understanding of the major variables that affect BAC after ingesting alcohol.

Cannabis—By contrast, little research has been conducted regarding estimations of the amount of cannabis used based on blood concentration levels.

The relationship between dose of THC and THC in the blood

In one study, subjects who took larger doses of smoked cannabis had only marginally higher levels of THC in their blood than those who received low doses (Hunault et al., 2014). This finding is consistent with a review of the literature by Ginsburg (2019) who concluded that doses of THC were not strongly correlated with THC in blood. A high degree of variability exists between people for THC blood concentration levels at different time points, given the same amounts used. Furthermore, THC blood levels are extremely different for ingested versus smoked cannabis. Formulas for the relationship between smoked cannabis and blood THC have been proposed but not independently validated. For example, Sticht and Kaferstein (1998) (reported in Grotenhermen et al., 2007) suggest that a 70 kg male who consumes 19 mg THC will have a blood serum concentration of 4.9 ng/mL (CI 3.1–7.7) after three hours. Extrapolation of this finding to whole blood, to females, other body weights, other time points and factors is problematic. As pointed out in this book, substantial variation exists for blood THC between individuals who are administered the same amount of cannabis. This formula must, therefore, be treated as speculative, as research validating this work, or that generalizes this formula to those with other conditions (i.e. sex, weight, metabolism, etc.), has not been adequately established. More research is needed on the time course of cannabis compounds in the body and factors related to these levels.

Variability among those who take the same dose of cannabis

Blood concentrations vary considerably among people who use the same amount of cannabis. For example, CV values were determined at four time points (up to 2.3 hours after smoking) for 19 subjects after smoking the same amount of cannabis (Hartman et al., 2015a). The CV values ranged from 46% to 82%, which indicates above average dispersion. The pharmacokinetics of THC produce large variations in THC blood between individuals, which makes back-extrapolation imprecise (Hartman et al., 2016). A peak level can vary substantially, often between 50 to 150 ng/mL in whole blood, depending on the person. For daily users of cannabis, THC levels can build up in the blood over time.

Post-mortem redistribution

Post-mortem refers to what happens to THC after death. After death, THC moves within the body, from high concentration areas to nearby low concentration areas (Anderson, 2016). THC largely moves from blood to body tissues over time in live subjects. After death, this process can be reversed and THC moves from body tissues into blood, resulting in increasing blood concentrations. Because different body tissues have different stores of THC, post-mortem THC concentration levels vary considerably depending on the body site from which blood is drawn. In a study of euthanized pigs injected with THC, Brunet et al. (2010) found that THC concentrations varied considerably, depending on where on the body blood was extracted from. Mantinieks et al. (2020) report that in one study that THC concentrations tend to be higher before death, but more research is needed on concentrations shortly after death. They also note that there is no obvious relationship between post-mortem and ante-mortem drug concentration ratios. Since post-mortem redistribution takes time, the interval between time of death and time when blood samples are obtained also plays an important role in THC concentration levels. This means that post-mortem THC levels do not properly reflect the levels just before death (Pélissier-Alicot et al., 1973). Saenz et al., (2017) found an inconsistency between post-mortem THC concentrations in the blood and the brain. Consistent with these findings was an earlier study of 10 deceased individuals (Mura, 2005), my re-analysis of this data also showed that the relationship between post-mortem blood THC and brain THC was poor (r^2 =.19). This finding suggests that blood samples of THC may not be an accurate measure of impairment. These factors have led a forensic toxicologist to conclude that post-mortem THC

concentration levels are more difficult to interpret than in live subjects (Anderson, 2016), although interpretation of blood THC in live subjects is also difficult.

Absorption and elimination of THC

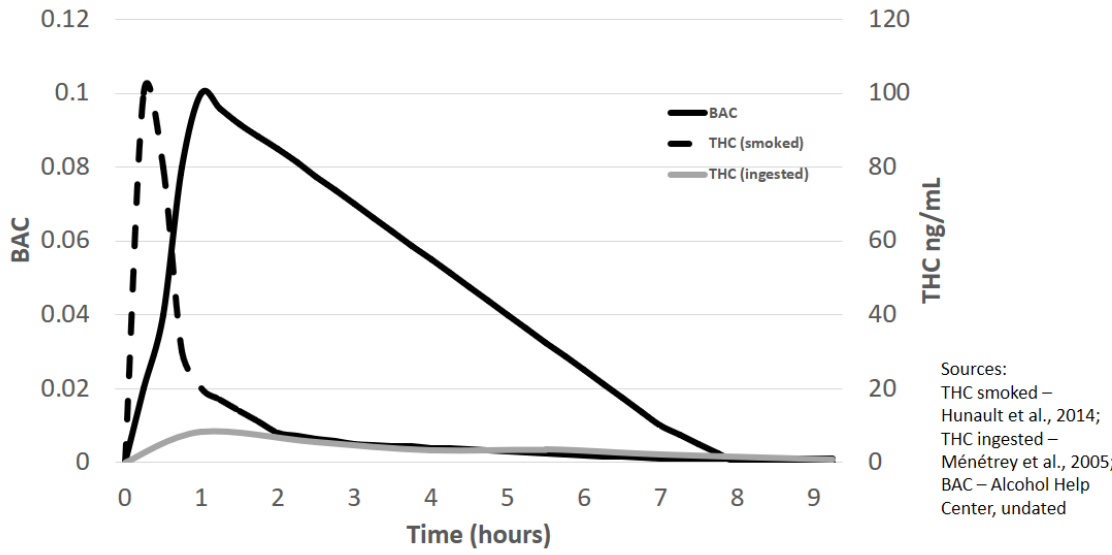
Figure 3 compares the absorption and elimination of THC from cannabis smoked or ingested and alcohol. This figure is adapted from serum to whole blood (using a very approximate conversion factor of 2/1) presented by Hunault et al. (2014). After smoking 50 mg THC of cannabis, on average THC levels rise very rapidly in blood and peak within three to 10 minutes. Around an hour after smoking, THC levels typically decline by about 90%, and then very gradually decrease. In contrast to alcohol, the elimination rate of THC from the blood is **not** constant over time. Elimination is rapid shortly after use, followed by a slow decrease as THC is re-released from fatty cells and metabolized. As pointed out by Huestis and Smith (2018), since THC is eliminated from the body in a nonlinear manner and can remain detectable for long periods of time, use of blood tests to assess effects of cannabis has major limitations.

The absorption and elimination numbers for cannabis ingestion from Figure 3 are based on a study by Ménétrey et al. (2005) for subjects who ingested at 45.7 mg dose of THC. In this situation, the average THC levels in whole blood were very low in the first hour after eating (the highest mean concentration was 8.4 ng/mL) compared to smoking. Subjects on average experienced gradual reductions to 3.5 ng/mL after 5.5 hours.

Most of cannabis, regardless of how it is taken (smoked or ingested), is eliminated from the body within five days in the form of two metabolites—hydroxy-THC and carboxy-THC (Sharma et al., 2012). Hydroxy-THC is eliminated more in feces, whereas carboxy-THC is eliminated more in urine (Sharma et al., 2012).

BAC absorption and elimination rates are based on a 175-pound man consuming five standard drinks very quickly. If many more drinks are consumed, the period of intoxication over a BAC of .05% would be much longer. In this example, an individual would be over a cut-off of .05% alcohol for about four hours. In contrast with cannabis, after absorption, BACs decline at a constant rate. This profile for alcohol elimination is much more promising than blood THC as a diagnostic tool for impairment.

Figure 3: Absorption and elimination of THC and alcohol



CONCLUSION

A chief pharmacokinetic difference between alcohol and cannabis is that alcohol is water soluble, whereas THC is fat soluble. The main implication of this difference is that alcohol in the blood has a strong relationship to alcohol in the brain, whereas for cannabis, the relationship between blood THC and THC in the brain is only strong shortly after use and only when smoked.

We have a good evidence-based understanding of the major variables that affect BAC after ingesting alcohol. Weight, sex and age are related to BAC levels, given the same amount of alcohol consumed. Individuals eliminate alcohol from the blood at a constant rate while THC is eliminated extremely rapidly from the blood shortly after smoking, followed by a period of slower metabolism. THC levels peak shortly after smoking cannabis but remain at low levels when ingested. THC concentrations in the blood are much lower when cannabis is ingested versus smoked. Variations between individuals in the elimination of THC are much greater for cannabis than alcohol. We know that alcohol is completely

eliminated from the body within a much shorter time frame than THC. The difference is especially great for daily users of alcohol versus regular cannabis users. Daily users of alcohol eliminate alcohol at a quicker rate than occasional users; however, for daily users of cannabis, THC can be detected in the blood for much longer periods of time than occasional users. All of these factors help to explain why BAC levels are a good measure for alcohol impairment but THC blood tests for cannabis are not.

CHAPTER 5

The acute effects of alcohol and cannabis on performance

In this Chapter, alcohol and cannabis are examined in terms of their acute (i.e. immediate) performance deficits. Studies reviewed in this Chapter include paired measures of performance measures and biological tests (i.e. the Breathalyzer for alcohol or blood, oral fluid and urine tests for cannabis) to assess the nature and strengths of their relationship. Self-reports by users and studies with direct measures of both performance deficits with BACs or THC concentrations for each subject are also reviewed in this Chapter. Case-control studies of the relationships of biological drug tests and crashes are reviewed in the next Chapter.

How do we best assess the accuracy of substance use tests for impairment? The best studies first determine a critical and meaningful criterion for performance deficits. Second, paired measures of drug concentration and performance level are taken and statistically analyzed to assess the relationship. A cut-off of concentration levels can be chosen base on a trade-off of sensitivity and specificity in comparison to the behavioural criteria cut-off.

I define impairment as meaningful decrements in psychomotor or other perceptual or cognitive functioning that increase safety risk. The most common form of impairment and the reason that people use drugs is based on immediate or acute effects. These immediate effects are the focus of impaired driving laws.

MEASURING THE AMOUNT OF ALCOHOL AND CANNABIS CONSUMED

Despite the fact that international units of analysis for alcohol are currently defined as grams of ethanol or litres of absolute alcohol, conveying the concept of a standard drink has been an uphill battle for both researchers and legislators. The definition for a standard drink varies considerably between countries. In Canada, a standard drink is defined as a 355 mL (12 ounces) beer at 5% alcohol, a 146 mL (5 ounces) wine at 12% alcohol, or 44 mL (1.5 ounces) of spirits at 40% alcohol (Canadian Public Health Association, 2006)—each equal in terms of absolute alcohol. However, research shows that people often do not consume alcohol in standard drinks. Wine and spirits are often free poured and beers come in a variety of sizes and alcohol contents that do not conform to standard drinks. The number of standard drinks recommended in terms of safe drinking guidelines also varies considerably (International Alliance for Responsible Drinking, 2017).

The challenges faced in terms of providing international standards are exacerbated with cannabis and illegal drugs. Cannabis comes in a variety of different concentration levels, estimated to average about 8.5% THC in cigarettes analyzed in 2008 (McLaren et al., 2008). Potency levels have been trending upward over time. In one experimental study, subjects were administered THC cigarettes of 23% potency (Hunault et al., 2014). Cannabis also comes in the form of hash, oil and synthetic products (Sativex). It can be smoked in joints of various sizes, through a pipe or vapourizer, or eaten. ***Titration*** of inhaled products in ***experiments*** has foiled some researchers (Hartman et al., 2015a), making it challenging to carry out a rigidly controlled study. Researchers have attempted to address some of these variations for determining dose amounts (Zeisser et al., 2008); however, much more investigation needs to be done.

A useful report on the equivalency of different types of cannabis, such as hash, buds/flowers, concentrates and other edibles was commissioned by the Colorado Department of Revenue (Orens et al., 2015). Based on a pharmacokinetic model, they estimated that one mg of THC in edible form is equivalent to 5.71 mg in smoked form. A large proportion of THC is destroyed during the smoking process. THC is actually created from the heat in smoked cannabis. For ingested cannabis to be most effective for its psychoactive effects, raw cannabis goes through an extraction process before use (Orens et al., 2015). Overall, there is wide variety of types of raw and processed cannabis, which provides complexity for any recommendations of psychoactive equivalency.

The best way to define cannabis is in milligrams of THC, because it combines both the percentage of THC and weight of the product into one measure. A standard single dose of cannabis commonly adopted for medical use is 10 mg THC, although there are no uniform dosing schedules (Government of Canada, 2016). Assuming an average joint weighs about .5 gm or 500 mg. A 500 mg joint of 12% THC would have approximately 60 mg of THC, - considered a high dose if smoked wholly by one person, and a very high dose if eaten. A moderate amount smoked is about 40 mg THC, and a small amount is about 20 mg THC. I support adopting an initial standard for a dose of cannabis of 10 mg THC as it will be simple for the public to understand.

Laboratory studies

Strengths and limitations

Laboratory studies are conducted in controlled environments and are most useful for identifying the precise nature of performance deficits produced by specific drugs. The best research design typically consists of a ***double-blind*** experimental approach where subjects are ***randomly assigned*** to a group-administered a drug or to a placebo (i.e. no pharmaceutical effect) group. Ideally, two identical groups of people living in a single environment are given two clearly different treatments, and then monitored for the possible differences of effects. This type of study has an experimental and control group that are assessed in terms of performance differences. This type of study has strong ***internal validity***—that is, the study design allows for strong inferences of cause and effect because the groups are equivalent in all other respects, except for the intervention. This type of validity should not be confused with validity of a drug test that was described in Chapter 2.

The main limitation of laboratory and simulator experiments relate to ***external validity*** issues or generalizability of findings because drug use and the driving environment in experimental designs may not reflect actual patterns of drug use and driving in the real world (Del Rio & Alverez, 1995a; van Laar et al., 1993; Volkerts et al., 1993). Performance deficits found in laboratory conditions may not translate into safety concerns in the real world for several reasons. For one, those who use cannabis may be unlikely to drive a car, possibly because the drug has a risk-aversive influence. Alternatively, the effects may not be substantial enough to meaningfully increase safety risk, or because individuals compensate for their condition. Furthermore, many of the performance tests assess

optimal performance of subjects and the findings likely aren't applicable to real-world conditions. For example, poorer memory recall is commonly reported effect from cannabis, often measured by timed tests for memory recall. A question of importance is how many names must drivers remember in order not to be considered impaired? Research has shown that memory and cognitive processes slow as we age. Does cannabis affect cognitive and memory deficits to a greater degree than would be expected in older people without cannabis? If the answer is no, then it seems problematic to claim such deficits constitute impairment. This speaks to the issue of a single threshold needed of performance for safe driving. Poor generalizability of laboratory research to real-world conditions can occur for other reasons, such as the use of naïve or occasional users rather than daily drug users, or duration and dosages of drugs that are different from how they are normally consumed (de Gier & Laurell, 1992; Del Rio & Alverez, 1995a).

A study by Leirer et al. (1989), is a good example that illustrates the potential challenges of translating findings from artificial laboratory studies to the real world: poor external validity. This study examined the relationships between age, cannabis doses and simulated aircraft performance with conditions in randomized order. An interesting finding of this study was that young subjects in the high-dose (20 mg) marijuana condition performed better than older subjects in the placebo condition at every time point (see Leirer et al., 1989; p. 1149). This conclusion is based on visual inspection of the means between groups as no statistical tests of significance were conducted to assess the likelihood this relationship was due to chance (this type of conclusion was likely of little interest to the authors). The authors did report significant ($p<.05$) performance decrements associated with cannabis at one hour and four hours compared to the placebo condition. One issue in this study is: how meaningful can cannabis deficits be in the real world when younger subjects in the high-dose marijuana condition did better than older subjects in the placebo condition at every time point? You might think from these results that young men are safer in the real world than older men; however, studies in real-world conditions have found young men have greater crash risk and job accident risk than older men (Insurance Institute for Highway Safety, 2013; Swedler et al., 2012). The findings from this study are a complete contradiction to what occurs in the real world with respect to age and accident risk. For reasons described above, findings in laboratory settings may not translate into real-world conditions.

Determining performance thresholds

Given the limitation of laboratory approaches, some researchers have specified the types of performance deficits that could translate into elevated crash risk in real-life situations that could be classified as impairment. Five key tasks or domains were identified by a panel of experts in the field (Kay & Logan, 2011):

(1) alertness/arousal
(2) attention and processing speed
(3) reaction time/psychomotor functions
(4) sensory-perceptual functions
(5) executive functions (e.g. memory and divided attention tasks)

The panel indicated that a psychoactive substance that "impairs performance in any of these domains at a magnitude known to be associated with increased crash risk is presumed to have a negative impact on driving safety" (Kay & Logan, 2011; p. 6). This panel has identified key domains that could unlock the discovery of the elusive behavioural "gold standard" of impairment from cannabis. However, the report did not go further and provide an ***operational*** definition of these thresholds, meaning there was no clear approach of how to best measure these deficits. The identification of these domains provides a useful guide on the types of deficits that should be included in laboratory studies of alcohol and drug effects. However, the extent to which each of these domains relates to crash risk is largely unaddressed. Some domains will likely have a more detrimental impact on traffic safety than others. For example, poor psychomotor functions that cause drivers to weave outside their driving lanes is more detrimental to driving safety than slower reaction times that cause drivers to drive more cautiously. Unfortunately, there has yet to be a proper analysis of the extent to which each of these domains is related to crashes, and performance cut-offs have not been proposed. A major issue is the challenge of deciding a threshold of these domains as they are typically measured as continuous variables. Optimal thresholds are based on a trade-off between sensitivity and specificity.

Driving a car is a complex task that requires various skills and adherence to rules of the road. Kay & Logan (2011) identified five ***cognitive*** skills domains (i.e. the process of thinking) needed for safe driving. Above all, driving requires focus on the changing environment and appropriate reactions to conditions. When this focus is compromised, the

likelihood of crashes increases. Some skills, such as defensive driving, are desirable but not considered essential for safe driving. Avoiding other cars' blind spots and driving extra distance behind a car are examples of defensive driving. Clearly, some drivers are better than others, but all drivers must meet a minimum threshold of safe driving. However, translating all these elements into concrete operational terms through performance tests is challenging. For example, memory tests are often used to measure performance deficits in relation to the acute effects of cannabis, yet we have not determined a specific threshold of memory that is needed for safe driving. Small differences between a marijuana and placebo condition can be detected in experimental studies, yet it is not clear that such differences are sufficiently large in magnitude to be classified as unsafe or impaired.

The preponderance of the evidence indicates safety risk is significantly increased within the domains identified by Kay and Logan (2011). Other effects of cannabis use such as red-eye, blood pressure and subjective effects are not specific performance deficits within these five domains and therefore are be **not** considered impairment, unless they can be established as strongly linked to meaningful performance deficits identified by Kay and Logan.

Another approach used to assess the degree of deficits from cannabis has been to draw direct comparisons of deficits from alcohol to those from cannabis. This can be accomplished by having subjects complete driver simulation tests under both alcohol and cannabis conditions. The amount of cannabis required for errors equivalent to those for alcohol at a particular BAC (often .05% or .08%) can be determined. Since substantial research evidence exists that these BAC concentrations are good thresholds for impairment (as described throughout this book) comparing errors from cannabis with alcohol is a suitable strategy. One study, described below, used this approach (Hartman et al., 2015b).

Acute symptoms and duration of impairment

Alcohol

The acute symptoms of alcohol are dose-dependent with symptoms such as increased talkativeness and sociability at low consumption levels (typically one or two drinks, <.05% BAC, depending on a person's weight and other characteristics), and symptoms of incoherent speech, staggering and memory loss at high consumption levels (typically five or more drinks, >.08% BAC). Alcohol at moderate levels (.05 BAC) can impair

both psychomotor skills and divided attention tasks, which increase the likelihood of accidents when operating complex machinery or driving a car. Tracking performance, which requires hand and eye coordination associated with safe driving, is sensitive to the effects of alcohol (Martin, 1998). There are individual differences in deficits caused by alcohol, related to tolerance and the ascending or descending BAC (Martin, 1998).

The duration of performance deficits depends on the amount of alcohol consumed and how long a person's BAC is above a particular threshold. The vast majority of laboratory-style studies on performance deficits from alcohol have paired BAC levels with performance indicators. An important research question is to establish a threshold of performance deficits whereby most individuals could be classified as impaired. Based on recommendations by Fell and Voas (2014) and an assessment of validity (see Chapter 2), .05% BAC is a reasonable cut-off.

Cannabis

Common symptoms of cannabis intoxication include impaired memory, drowsiness, euphoria, heightened perception, increased appetite and distortion of time (Hall & Solowij, 1998). Numerous laboratory-style studies and reviews have been conducted on the acute effects of cannabis on performance. A review article published over three decades ago provided an assessment of the acute effects of cannabis on driving, which have not been refuted by subsequent research (Moskowitz, 1985). Coordination, tracking, perception and vigilance were all negatively affected by cannabis. Limitations noted by this author are that a clear determination of the magnitude and nature of psychomotor performance is unknown, and studies of heavy chronic users are lacking. Unfortunately, these same limitations could be said to be present in existing research today. Several dimensions of performance were examined in the 1985 review: coordination, reaction time, tracking, as well as sensory and perceptual functions. A review article concluded that cognitive deficits are associated with acute effects, but fewer studies show motor deficits similar to those found for alcohol (Prashad & Filbey, 2017). A review paper by Bondallaz et al. (2016) found evidence of increased lane weaving, as well as longer distances behind vehicles, under cannabis conditions. Certainly, lane weaving would constitute impairment when drivers weave outside of their own lane. Another systematic review (Broyd et al., 2016) reports that the wide ***heterogeneity*** of studies (in terms of cannabis exposure, samples and measures) makes it challenging to draw meaningful conclusions, as the studies

are very different from one another. These authors evaluated several cognitive domains and found strong scientific evidence that the acute effects of cannabis lead to deficits in verbal learning and memory, attention and psychomotor function. The overall research shows that cannabis causes performance deficits; however, the establishment of performance thresholds that could constitute impairment similar to the effects of a BAC of .05% has not been properly addressed.

Two common observations of interest for altered driving under the influence of cannabis are slower speed and lateral control. These outcomes were the focus of a study on the effects of cannabis in simulated driving (Brands et al., 2019). Mean speed differed between the two cannabis groups (high and low doses) and the placebo but lateral control was unaffected 30 minutes after use, with those in the cannabis group driving significantly slower. These findings raise issues of the impact of slower driving for traffic safety. Ginsburg (2019) quantified the distances, noting the maximal study found weaving to be only 8 cm, which constitutes only about 2% of the lane width. The above studies suggest harm avoidance effects from cannabis and the magnitude of deficits from cannabis is not substantial.

Generally, based on subjective effects, a peak psychoactive high is experienced after smoking cannabis within 30 minutes, which lasts approximately two hours with a return to normal within four hours (Grotenhermen, 2003; Kelly et al., 2004; Raemakers et al., 2004). Research shows that a high for smoked cannabis is nearly certain within a one-hour period if smoked, and the majority of people will not be experiencing any symptoms after four hours. A shorter average duration of 45 minutes for being high was noted in one study for a 9 mg THC cannabis cigarette (Harder & Rietbrock, 1997).

Typically, studies have only been able to detect concrete performance deficits within the first hour after smoking. Although in some studies, performance deficits have been found at longer time points after smoking, these findings have to be excluded due to methodological weakness or they use measures that are not concrete, such as subjective effects. Some researchers have not conducted statistical comparisons between subjects at particular points in time (e.g. see Spindle et al., 2018) and therefore we cannot conclude that deficits exist at these time points.

In another study, the authors speculated that they failed to find significant declines in SFST measures because they administered the tests at 1.5 and 3.5 hours after smoking (Newmeyer et al., 2017b). Peak highs are longer after ingesting cannabis, typically noted at

between one to three hours, and declines to low levels within six hours (Grotenhermen, 2003.)

In a study by Curran et al. (2002), the effects of 15 mg and 7.5 mg *oral doses* of THC were compared with placebo capsules, in this cross-over design. Subjects were assessed with 13 different performance measures at and one, two, four, six, eight, 24 and 48 hours after cannabis ingestion. The authors found significant performance deficits for six of 13 measures[1] for ingested cannabis two hours after administration in the high dose (15 mg THC), but not the low dose, compared to three deficits at one hour, two deficits at four hours, one deficit at six hours and no deficits at eight and 24 hours. The greatest deficits in performance occurred at two hours with six of 13 measures statistically worse at this time point.

The breadth of performance measures taken in this study are numerous compared to other studies. As well, the authors reported pairwise results at different time points, useful statistical tests for assessing the duration of performance deficits but rarely reported. For these reasons, I have summarized the findings in **Table 8**. A shortcoming of this data, however, is the findings cannot be generalized to smoked cannabis because cannabis was ingested in this study. Statistical significance of comparisons of performance tests between each dose (7.5 mg and 15 mg THC) and the placebo condition at one, two, four, six, eight and 24 hours after ingestion. At six and eight hours, only two performance measures were significant: choice reaction time (eight hours) and prose recall (six hours). The lack of significance at six and eight hours for all but two variables suggests much reduced performance deficits at these time points. Choice reaction time was statistically significant eight hours in the low-dose condition but not significant at any other time point. The lack of consistency of findings across time points is suggestive that significance at eight hours may be a Type I error, and not meaningful. On the other hand, prose recall was significantly worse in the high dose condition at two, four and six hours, suggesting that memory can be affected by ingested cannabis for up to six hours with higher doses. Overall, one can conclude from this study that performance deficits are unlikely under either a 7.5 mg or 15

[1] Bushke selective reminding, Digit cancellation tasks, Double target cancellation, Simple reaction time, Prose recall, Delayed recall

mg condition at eight hours after use. Peak deficits occur at about two hours when cannabis is ingested. In addition to comparisons in Table 8, subjects were also asked about subjective effects. At six and eight hours, for the 15 mg condition "feeling stoned" was statistically significant. As previously mentioned, subjective effects are not easily translated into measurable performance deficits and therefore are difficult to interpret in relation to safety. Based on this study by Curran et al. (2002) two types of deficits were noted in the first hour for both doses of ingested cannabis: Baddeley reasoning and Double target cancellation. For the Baddeley reasoning test, subject are asked to indicate whether a variety of statements are correct, and correct scores are summed at the end of three minutes for a composite score (Baddeley et al., 1968). For example, A follows B – BA (correct response is true) and B precedes A – AB (correct response is false). On one hand, this type of task appears to measure attention and processing speed, a domain identified by Kay & Logan (2011) as required for safe driving, and therefore could be a useful scale to identify impairment. On the other hand, since this particular test is timed where subjects are required to perform at optimal levels, and in the real world may be able to compensate for such slower processing speed. We don't know whether such findings have external validity. The Double target cancellation is typically used to identify visual scanning deficits where subjects are asked to cross out the letters C and E from a six-line paragraph. This test appears to measure speed the domain sensory-perceptual identified by Kay & Logan (2011) as required for safe driving; however, it too is a timed test. Again, as previously described, there is a need to create performance measures that have good external validity for impairment related to safe driving. Such measures are critical for assessing the validity of any biological test.

Table 8: *Significant simple effect differences between placebo and drug conditions (7.5 mg and 15 mg THC) for various tasks, adapted from Curran et al. (2002)*

Measures	1 hour		2 hours		4 hours		6 hours		8 hours		24 hours	
Performance tests	**7.5 mg**	**15 mg**	**7.5 mg**	**15 mg**	**7.5 mg**	**15 mg**	**7.5 mg**	**15 mg**	**7.5 mg**	**15 mg**	**7.5 mg**	**15 mg**
Bushke selective reminding	ns	ns	ns	**	ns	ns	ns	ns	ns	ns	ns	ns
Rapid visual information processing	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Baddeley reasoning	**	**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Serial sevens	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Choice reaction time	ns	*	ns	ns	ns	ns	ns	ns	*	ns	ns	ns
Digit cancellation tasks	ns	ns	**	**	ns	**	ns	ns	ns	ns	ns	ns
Double target cancellation	*	*	ns	*	**↓	ns	ns	ns	ns	ns	ns	ns
Simple reaction time	ns	ns	ns	*	ns	ns	ns	ns	ns	ns	ns	ns
Prose recall	ns	ns	ns	***	ns	***	ns	***	ns	ns	ns	ns
Delayed recall	ns	ns	ns	*	ns	ns	ns	ns	ns	ns	ns	ns
Perceptual priming	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Verbal fluency	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Gibson's spiral maze	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

*p<.05 **p<.01 ***p<.001, ns – not significant ** ↓ deficits were significantly greater in the placebo.
Note: Relationships not reported are assumed to be not significant.

In 2005, a panel of experts on driving under the influence of cannabis made recommendations for objective criteria to determine impairment by cannabis (Grotenhermen et al., 2005 and 2007). Their analysis found maximum performance deficits in 64% of test results at 20 to 40 minutes after smoking, which compared to 35 to 40% of test results showing any performance deficits between one and 2.5 hours after smoking. Time period after use is an important variable for likely deficits, but variability between individuals is great, making it difficult to draw reasonably precise conclusions on the validly of blood tests for impairment.

A finding of Grotenhermen et al. (2007, p. 1910) was: "A comparison of ***meta-analyses*** of experimental studies on the impairment of driving-relevant skills by alcohol or cannabis suggests that a THC concentration in the serum of 7–10 ng/mL is correlated with an impairment comparable to that caused by a blood alcohol concentration (BAC) of 0.05%". However, this conclusion was based primarily on laboratory studies where no blood tests were conducted, a limitation acknowledged by the authors. In my opinion a conclusion about an association of blood tests for THC and impairment cannot be justified unless direct comparisons are conducted between the two—and no studies are cited where these comparisons were done. Furthermore, numerous studies presented in this book show that THC concentrations vary considerably between subjects administered the same dosage of THC. A common principle of research is that one should not draw inferences about findings (i.e. generalizations) to a different population than from the studies in which the participants of the study were selected. The approach in this paper lacked external validity, a fundamental principle of science.

The above studies have several notable limitations. We do not have a clear idea of the amount of cannabis needed to produce impairment and how to measure impairment. Although we can provide some general conclusions based on averages, variations among individuals is large. For the laboratory studies, performance tests were usually performed within the first hour after cannabis administration (Grotenhermen et al., 2005). It appears that performance deficits can meet a threshold of impairment a shortly after use. One difficulty in determining impairment is related to the failure of studies to make any distinction between performance deficits and impairment. There are some studies that compare biological test measures with performance that are reviewed in greater depth later in this Chapter.

STUDIES ON THE RELATIONSHIP BETWEEN PERFORMANCE DEFICITS AND BIOLOGICAL TESTS

In the section of Chapter 2 titled "The purpose of biological tests," I described the epidemiological process of assessing the validity of diagnostic tests to assess impairment based on laboratory findings. Studies on how researchers applied this method for alcohol and cannabis impairment were examined. This ideal process involves the following steps:

- Create a gold standard to define cannabis impairment in terms of behavioural performance deficits.
- Conduct paired biological drug tests with the gold standard of impairment.
- Determine the best cut-off that reflects an acceptable trade-off between sensitivity and specificity for a threshold of impairment.
- Calculate Kappa, which ideally should be over .75 for excellent agreement.

Unfortunately, studies that used these ideal methods were not found. Rather, laboratory studies typically assess the relationship between drug concentrations and performance deficits as continuous variables, without attempting to delineate an impairment cut-off. Although such studies an understanding on the nature and magnitude of the relationship between performance and substance concentrations, they are less helpful for arriving at an evidence-based per se limit for impairment.

Alcohol

Performance deficits have been detected at low levels (< .02% alcohol) (Ogden & Moskowitz, 2004), but driving at these levels has not been shown to be detrimental. In an earlier review paper on this topic, Moskowitz and Florentino (2000, abstract) concluded that "alcohol impairs some driving skills beginning at any significant departure from zero." Yet, when examining a summary of their review of laboratory findings on behavioural test results of performance from with BACs between .02 and .029%, about five times as many studies reported no impairment compared with impairment at this range. The fact that the majority studies found no measurable effects at these BAC levels suggests that the magnitude of any performance deficits found at this level does not meet a threshold of meaningful safety risk. Most studies have found no performance deficits at these levels. As

well, no information is provided on whether there were performance improvements at this range. Often authors don't even test for possible improvements at this range, using a statistical procedure known as ***one-tailed statistical test***, common in some disciplines, such as psychology (the discipline of Herbert Moskowitz), but rarely used in other disciplines, including epidemiology. Epidemiologists argue that one-tailed statistical tests can obscure important findings. Also, this review paper and many others on BAC level and impairment did not classify subjects in terms of sensitivity and specificity by choosing an optimal cut-off to assess validity. In any case, conclusions from such studies do not reflect the preponderance of the research and are likely not relevant to the real world. One study that statistically examined possible improvements at .02% BAC did find performance improvements for throwing darts (Reilly & Scott, 1993).

The majority of research reports a strong negative linear relationship between BAC level and performance, meaning that as BAC levels increase, performance decreases and that the relationship is linear. For example, Dawson and Reid (1997) found a strong linear relationship between the two ($p<.05$, $r^2=.69$). Although the vast majority of studies have demonstrated a strong relationship between BAC levels and performance, none were found that examined the validity of a .02% cut-off for impairment. Data from existing research that compare performance and BAC levels as a linear relationship can be misleading, if other types of curves are better fits for the data. For example, in the study by Dawson and Reid (1997), drivers at less than .02% alcohol performed better than they did at baseline. Drivers at .05% alcohol performed worse (about 96% of baseline) and those at .08% alcohol performed much worse (about 90% of baseline). This data does not support deficits at .02% alcohol as no performance deficits were found at this level. Studies such as these do not support a threshold because data is presented as a continuous measure and performance deficits that constitute impairment are not operationally defined. Such studies illustrate the limitations of describing performance at these levels as impairment. Studies on low BAC cut-offs and impairment did not classify subjects in terms of sensitivity and specificity as I recommend. The vast majority of studies have demonstrated a strong relationship between BAC levels and performance but have not shown performance deficits are meaningful at low BAC levels but practically all research shows levels at .08% and higher represent substantial and meaningful declines in performance.

Cannabis

A question of importance is: what is a low dose for cannabis? In fact, there is no accepted definition of a low dose, and the effect of cannabis on one individual may be quite different from that of another. Anecdotal evidence indicates micro-dosing cannabis (taking the lowest dose possible to achieve a particular effect) has increased in popularity, especially for medical issues, such as anxiety. The extent of micro-dosing in the general population is largely unknown.

Like alcohol, prevailing research suggests cannabis produces cognitive and behavioural deficits in a dose-related manner (Hall & Solowij, 1998). This is especially true when cannabis is ingested. However, research is too limited to draw any conclusion on how low doses of cannabis affect performance. At low doses of cannabis, defined by the authors as administration of nine to 18 mg THC, a review study did not find performance deficits between 2.5 and 12 hours after use (Grotenhermen et al., 2005). Given the difficulty of researchers to provide a meaningful operational definition of cannabis impairment, mixed findings of many studies on the acute effects of cannabis in terms of performance deficits, and the weak validity of DRE assessments for recent use, low doses do not appear to produce meaningful performance deficits. As pointed out in this book, effects differ depending on whether cannabis is smoked or ingested, or the user's previous experience with cannabis.

Another issue is: what is the relationship between THC blood levels and dose amount? Hunault et al. (2014) describes a low dose at 29 mg THC when smoked, and found serum blood levels peaked on average at about 140 ng/mL THC (very roughly equivalent to about 70 ng/mL in whole blood) and after two hours, THC levels appeared to peak at about 210 in the high-dose (69 mg THC) condition. Overall, the research is sparse in terms of how low doses affect performance but THC levels do appear to get fairly high at low doses when cannabis is smoked. It does not appear that there is a direct correspondence between THC concentrations smoked and THC blood levels. For example, a doubling of the concentration smoked will yield less than double the THC concentration level.

Performance and THC in blood

I found two review papers that made recommendations of THC blood level ranges associated with impairment and therefore these papers deserve special attention described

below (Grotenhemen et al., 2007; Hartman & Huestis, 2013). Both review articles included laboratory style and observational studies.

Grotenhemen et al. (2007)—Grotenhemen et al. (2007) proposed a possible per se limit of 7–10 ng/mL THC in serum, which they indicate is equivalent to 3.5–5 ng/mL THC in whole blood. This expert panel reviewed both laboratory studies on cannabis and performance and epidemiological studies of cannabis and accident risk and weighed the laboratory studies heavily in arriving at their conclusion above. In their review, they found 87 studies of cannabis administration and a variety of performance tests. These studies provide tangible evidence of performance deficits from the acute effects of cannabis, summarized earlier in this Chapter. Unfortunately, as previously discussed in this Chapter, few of these studies included blood tests for THC, meaning that direct measures of blood THC with performance could be not be accurately assessed. Instead, the authors estimated blood THC concentrations of subjects in these studies based on the dose, and other factors (weight and sex were noted). The authors did acknowledge substantial within- and between-subject variability in THC blood levels over time and that this was a limitation of their approach. In my opinion, this approach is scientifically unsound and the conclusions above cannot be justified by these methods.

Hartman and Huestis (2013)—These authors conclude that recent smoking of cannabis and 2–5 ng/mL THC in whole blood are associated with substantial driving impairment based on a review of both laboratory studies. This paper did not attempt to determine THC blood levels from the laboratory studies reviewed. No findings from any laboratory study with paired blood THC and performance measures were noted in this review. Therefore, it must be assumed that the laboratory studies mentioned in this review refer to the acute effects of recent smoking and not impairment related to THC from blood tests.

Some empirical studies that examined the relationship between paired measures of THC in blood and performance are reviewed below, presented in alphabetical order of first authors. Since smoked and ingested cannabis has different durations of performance deficits, they are examined separately.

Smoked cannabis

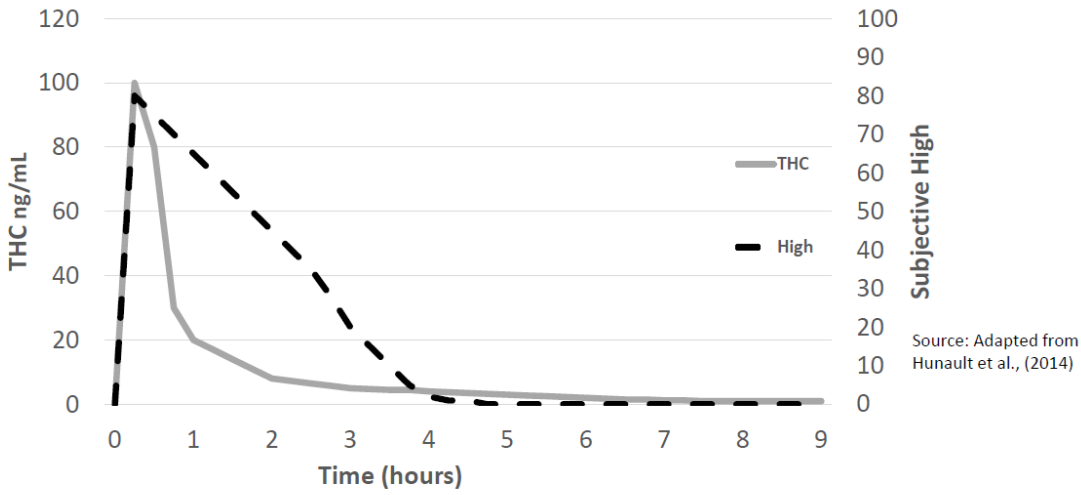
Hartman et al. (2015b)—This study has a randomized, double-blind, and placebo-controlled research design—a classic experimental approach. The outcome measures were

lateral control, such as weaving, in a very realistic driving simulator. They were also able to calibrate driving performance with blood THC levels in cannabis through comparison to alcohol-impaired driving. They noted that 52.6% of their subjects showed evidence of titration (or a subject inhaling more or less cannabis to obtain the optimal dose), which may help explain the substantial variations between subjects in THC blood concentrations at the same time points. The authors clearly found deficits related to THC blood levels. They concluded that blood THC concentrations of 8.2 ng/mL and 13.1 ng/mL correspond to deficits from alcohol of .05% and .08% respectively. This research stands out as an exceptional contribution because THC concentration cut-offs were calibrated against typical BAC cut-offs. With such data, the authors easily could conduct an additional study on the validity of any THC cut-offs for performance deficits. Other studies, described below, also took paired THC blood and performance measures, but none of the studies below provide an assessment of the validity of different cut-offs for impairment based on methods suggested in this book.

Hunault et al. (2014) – In this study, the relationship between three different THC potency cigarettes (from 29 mg to 69 mg THC) and subjective reports at various time points were examined among 24 recreational users. **Figure 4** shows a comparison of the THC[1] levels and levels and subjective levels of intoxication with a 69 mg cannabis cigarette. The peak high and peak THC concentration levels occurred at a similar time at under 30 minutes after smoking. However, THC level declines much faster than the decline in feeling high, an observation noted by Moskowitz over 30 years ago (Moskowitz, 1985). It is clear that a relationship exists between THC levels and subjective high; however, the relationship is strong within the first hour after smoking, and declines greatly after one hour and levels level off at about 10–20 ng/mL, followed by a gradual decline in THC concentrations. This data shows subjective effects, not performance deficits. As noted earlier in this Chapter, subjective effects should not be considered impairment.

[1] Hunault et al. (2014) assessed THC with serum. Figure 4 has been adapted to whole blood levels from serum using a crude whole blood/serum conversion ratio of .5.

Figure 4: *The relationship between THC concentrations in whole blood and subjective feelings of being high for* ***smoked cannabis*** *of 69 mg THC*



Selection of a THC cut-off within the first hour after use of over 10 ng/mL during the steep rise and decline will have better overall validity for impairment than a lower cut-off within an area of a more gradual decline. Overall, higher thresholds will yield better specificity and lower sensitivity. The best overall accuracy of THC in blood for impairment, based on this study may be in the range of 10–20 ng/mL which typically occurs within two hours after smoking—a period some have noted represents performance deficits. Accuracy can be established through analysis of the raw data with an approach known as ***Receiver Operating Characteristics (ROC).*** This approach involves plotting sensitivity (y-axis) against 1-specificity (x-axis) in a Figure and choosing an optimal cut-off based on the relative consequences of false positives and among the options in the upper left hand half of the Figure (Campbell & Freeman, 2008).

Although this study has several merits, findings were presented with summary statistics of means. Unfortunately, measures of central tendency such as these tend to obscure variations between subjects, known to be extreme (Moskowitz, 1985). Individual data is needed to properly assess the validity of a particular THC cut-off in terms of impairment. Moreover, from this data, we do not know what level of subjective high could

constitute impairment. Knowledge of the variability between individuals and a good benchmark for performance deficits that constitute impairment are needed in order to properly assess the validity of a given cut-off for impairment, which was not the purpose of the paper by Hunault et al. (2014). Validity as described in this book is non-existent in the literature, which means that cut-offs for cannabis impairment are based on a weak scientific foundation. In order to achieve this goal, individual-level data is required, not descriptive summary statistics. The approach used by Hunault et al. (2014) is not a substitute for the methods to assess validity described Chapter 2, but the study provides some empirical evidence of a likely valid cut-off.

Khiabani (2006)—In this study, 456 blood samples positive for THC only were identified from Norwegian drivers suspected of driving under the influence of drugs. The authors found a significant relationship between the proportions of subjects with judgements of impairment by police and higher THC positive groups. For example, they found that 38% of those with THC levels less than .7 ng/mL were judged as impaired compared to 57% for those with more than 10.2 ng/mL. Although this study does affirm a positive relationship between THC concentrations in blood and the likelihood of being assessed as impaired, this relationship is too weak to establish an accurate per se limit.

Lenne et al. (2010)—This double-blind ***counterbalanced design*** study aimed to assess the performance effects of cannabis under placebo, low and high-dose conditions. Driving simulations in the cannabis dosage conditions were related to decreased speed and longer reaction times compared to the placebo condition, and blood tests confirmed higher average THC concentration in the low (7.4 ng/mL) and high-dose (12.01 ng/mL) conditions. Like most other studies, however, performance thresholds that might constitute impairment were not established and direct measures of paired blood and performance measures were not reported.

Ramaekers et al. (2006)— In this double-blind ***cross-over*** design of 20 subjects in three smoked doses of cannabis (25 mg, 50 mg THC, and a placebo), serum blood THC were paired with performance measures taken at baseline and nine-time points afterwards. Three performance measures were used: distraction (a critical tracking test), a measure of impulse control (the stop-signal test), and a measure of planning and problem solving (the Tower of London decision-making test). The authors concluded that serum concentration levels between 2 and 5 ng/mL could establish the lower and upper range for THC

impairment. This study deserves attention because recommendations were made and the findings have been influential in the field.

Although the study design was good, errors were made in the analysis that do not justify the overall conclusions. In particular, the authors used an improper statistical procedure that increases the likelihood of finding statistical significance and improperly interpreted the meaning of the relationship. The authors presented scatter plots of log-transformed THC serum concentrations (not actual THC levels) and performance measures. The correlation coefficients from the regression analyses between log-transformed THC and these three performance measures were poor with r-values between .15 and .4, which means between 2% and 16% of the variation in blood tests were related to the performance measures. These low r^2 values were in fact inflated by taking 11 different measures of the same individuals, a procedure that reduces the variability of the sample, leading to erroneously high correlations and violation of the assumption of independent measures required for the statistical test (see Chapter 3 of this book, "Summary Statistics and correlations"). The proper statistical procedure for this kind of data is a mixed repeated measure Analysis of Variance (ANOVA). This study shows that blood THC levels are not an accurate predictor of the magnitude of performance deficits for these three measures. As well, the measures used may not translate into road safety concerns in the real world, a limitation that the authors do acknowledge. The authors' overall conclusion that serum concentration levels between 2 and 5 ng/mL could establish the lower and upper range for THC impairment is not justifiable based on analytical shortcomings and inaccurate interpretations of the results.

Schwope et al. (2012) — This study administered a cannabis cigarette containing 54 mg of THC to 10 *heavy and chronic* cannabis smokers were and followed up with performance and THC blood tests over six hours. Performance-based on critical tracking and divided-attention tasks did *not* significantly change from baseline to 15 minutes after smoking. Blood THC concentrations decreased rapidly in the first hour after smoking, similar to finding reported by Hunault et al. (2014). The authors created a cannabis influence factor scale, based on combinations of THC, hydroxy-THC and carboxy-THC; however, they did not find this scale was useful for quantifying psychomotor impairment. This latter finding is not surprising, given that no meaningful performance deficits were found after cannabis administration.

Arkell et al. (2021)—A poor relationship was found between impairment and blood.

Ingested cannabis

Curran et al. (2002)—Performance measures form this study at different time points after ingestion were described earlier in this Chapter. Average blood plasma THC peaked at about 4.5 ng/mL (much lower THC than expected from smoked cannabis) at two hours and declined close to zero by eight hours. In terms of blood THC over time the findings from this study are consistent with Ménétrey et al. (2005), described below.

Ménétrey et al. (2005)—In this double-blind cross-over study, 10 subjects were administered hemp milk of 16.5 and 45.7 mg THC (the latter dose is very high), synthetic THC (at 20 mg THC) and a placebo. The authors took measures of both THC and hydroxy-THC, a unique approach, and incorporated an outcome of willingness to drive under different conditions. THC concentrations were very low; around 8.4 ng/mL at peak levels and declined very slowly thereafter for the 45.7 mg THC dose. Similar to studies of smoking cannabis, extremely large variations between subjects in THC and cannabinoid levels (hydroxy-THC and carboxy-THC) were found at the same time points after smoking. For example, the range in THC levels at 2.5 hours was from 1.6–9.0 ng/mL in the high-dose condition, and the ranges for hydroxy-THC at all time points were also extreme.

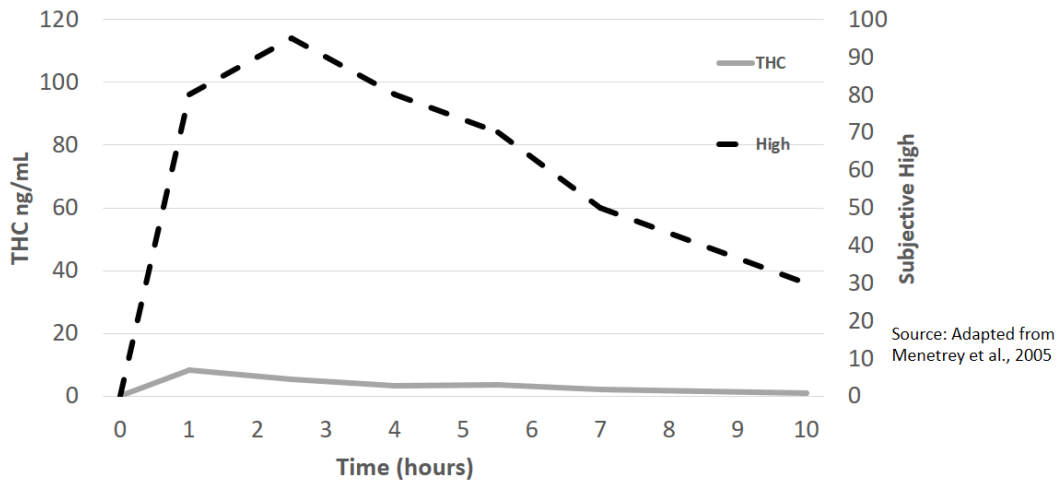
The relationship between average THC levels in blood (for the 45.7 mg dose) and subjective reports of feeling high are shown in **Figure 5**. The subjects also gave subjective reports of how high they felt at different time points. I have converted the ratings from a 10-point scale to a 100-point scale to allow rough comparisons with the Hunault et al. (2014) study. Average subjective highs of at least 80/100 were found between one and four hours.

The following conclusions can be drawn when comparing the results of with ingested cannabis (Ménétrey et al., 2005) with smoked cannabis (Hunault et al., 2014). THC concentrations in the blood peak much higher for smoked cannabis than when ingested. Higher THC doses for both smoked and ingested cannabis do not affect subjective effects proportionally. For example, twice the dose of cannabis does not mean performance will be twice as bad. However, for ingested cannabis, more proportional decrements in subjective effects were found for the strongest concoction. Subjective ratings of being high peaked at just over 2.5 hours after use and lasted up to 10 hours. Most participants indicated that they would not drive a friend to a party after 10 hours but statistical tests of significance were not conducted in this study. Also of note, two subjects were withdrawn from the study due to adverse side effects of anxiety or vomiting. This study raises issues regarding cannabis and driving. It appears that ingesting cannabis may produce deficits over

a longer period than smoking with more intense effects at higher doses, despite the fact that subjects may have lower THC concentration levels than would occur from smoking.

Ménétrey et al. (2005) study highlight the possibility that hydroxy-THC can cause performance deficits. Recall from Chapter 4 that the liver converts THC into hydroxy-THC, which has psychoactive properties, possibly more potent than THC itself. Hydroxy-THC levels exceeded THC levels at every time point, peaking at 12.8 ng/mL at 2.5 hours, the same time point of the greatest subjective high. At 10 hours in the high-dose condition, average THC levels were only .9 ng/mL, whereas hydroxy-THC levels were 2.5 ng/mL. THC and hydroxy-THC levels combined provided the best estimate of impairment. The Ménétrey et al. (2005) findings implicate hydroxy-THC as an important psychoactive metabolite for impairment, more research is needed on the role of hydroxy-THC in impairment.

Figure 5: *The relationship between THC concentrations in whole blood and subjective feelings of being high for ingested cannabis of 45.7 mg THC*



Ranganathan et al. (2006)—In this review of the literature, both smoked and ingested cannabis effects were studied. These authors conducted a review of the acute effects of cannabis on memory and noted that cannabis is related to increases in intrusion errors, recall of information not presented. Another interesting finding of this review was their conclusion that cannabis effects are most intense when administered intravenously,

less intense when smoked and least intense when taken orally. Like conclusions by Grotenhermen (2003), they noted that ingested cannabis is longer lasting than the other two methods of administration.

Summary

Interestingly, the ratios of average blood THC levels and doses of THC (i.e. high, medium and low) do not appear to vary in the same proportions. This observation is based on a study by Hunault et al. (2014). Inspection of the figures in Hunault et al. (2014) suggests peak average THC serum levels in the high THC condition (69 mg) cigarette was about 210 ng/mL, whereas in the low level (29 mg) cigarette, the peak was about 140 ng/mL. Exact numbers were not presented in this study. Titration may be an explanation for these divergent ratios. When eating cannabis, THC levels in blood tend to reach a much lower peak level at about one hour after ingestion.

None of the studies above, except Hartman et al. (2015b), made any attempt to define the meaning of impairment. Rather, any significant performance deficit was interpreted as impairment. Whether these measures translate in significantly worse driving is unknown. Some of the studies, such as Curran et al. (2002), had a good selection of performance measures taken at several time points after use.

Performance and THC in oral fluids (OF)

Fierro et al. (2014)—The authors examine the relationship between oral fluid (OF) tests and observations of impairment by police officers. Observations were based on a roadside survey of over 3,000 Spanish drivers. The police officers received 20 hours of training, which included identification of 31 signs of being under the influence of cannabis. OF concentration levels based on confirmatory tests of THC were categorized into five ordered ranges. This is the only study I am aware of that directly compares OF concentration categories with observations of impairment.

I have re-analysed the data from the Fierro et al. (2014) study to illustrate the type of analyses that are helpful for deriving evidence-based per se limits to detect cannabis impairment, using epidemiological methods to assess the validity of OF cut-offs of 25 and 100 ng/mL THC against the standard of observations by trained police. **Table 9** below shows the relationship between OF tests at a cut-off of 25 ng/mL. This analysis shows that at two cut-offs, accuracy is good, sensitivity is poor and specificity is good—largely influenced by

the very high proportion of subjects with no THC present. Positive predictive value, the likelihood that someone who tests positive will show any sign of impairment, is poor at 19.6% with a 25 ng/mL cut-off and 22% at a 100 ng/mL cut-off. In the above examples, using expert detection of **any** signs of impairment and an OF cut-off levels of 25 ng/mL and 100 ng/mL, both Kappa values are below .4, which represents poor agreement (Gordis, 2014). Overall, the relationship is unacceptable. The improvement in accuracy at a cut-off of 100 ng/mL versus 25 ng/mL is minimal. If a valid cut-off for oral fluids to assess impairment exists, the concentration level is likely substantially greater than 100 ng/mL. No biomarker cut-off from cannabis has been validated for impairment. The definition of impairment by cannabis by behavioural criteria also has been elusive and no gold standard similar to SFST for alcohol exists. A combination of several observational criteria rather than any observational sign might have better validity for a threshold of cannabis impairment.

Table 9: *The relationship between any impairment signs and oral fluid tests for THC at 2 cut-off levels**

25 ng/mL cut-off	Any sign	No sign	Total	100 ng/mL cut-off	Any sign	No sign	Total
>25 ng	27 (a)	111 (b)	138	**>100**	20	69	89
OF <= 25 ng	26 (c)	2235 (d)	2261	**<= 100 ng**	33	2277	2310
Total	53	2346	2399	**Total**	53	2346	2399

**Detailed calculations for 25 ng/mL:*
(a) = (49*14.3%) + (89*22.5%) = 27
(b) = (89+49) – 27 = 111
(c) = (2146*1%) + (34*2.9%) + (81*4.9%) = 26
d) = (2146+34+81) – 26 = 2235

Example 1 at 25 ng/mL—Accuracy = 94%, Sensitivity = 27/53 = 51%, False negatives = 26/53 = 49%; Specificity = 2235/2346 = 95%, False positives = 111/2346 = 5%; Positive predictive value = 27/138 = 19.6%; Kappa = .256 (95% CI, 0.175 to 0.343)

Example 2 at 100 ng/mL—Accuracy = 96%, Sensitivity = 20/53 = 38%, False negatives = 33/53 = 62%; Specificity = 2277/2346 = 97%; False positives = 69/2346 = 3%; Positive predictive value = 20/89 = 22%, Kappa = .261 (95% CI, 0.163 to 0.359).

Ramaekers et al. (2006)—In this study, both serum blood tests and oral fluid tests were taken, along with three measures of performance at 10-time points, previously described above. No recommendations were provided with respect to impairment by oral

fluids; however, findings from this study should be given little weight based on the flaws previously described.

Performance and Carboxy-THC in urine

I am not aware of any laboratory studies on the relationship between urine test results and performance deficits. Given our current knowledge of the detection periods for components and metabolites in urine, it is unlikely that such research would yield worthwhile findings**.** Compounds are detectable in urine two to six hours after the use of cannabis and other drugs (Swotinsky, 2015). After smoking cannabis, the most intense high occurs within the first hour or two, precisely the period of most relevance to detect impairment.

Summary of blood, oral fluid and urine tests to detect impairment

In Table 6 (Chapter 3), the detection periods after last cannabis use, based on blood, oral fluid and urine tests, were provided. In this Chapter, typical periods of performance deficits that could constitute impairment were described. When smoking cannabis, the maximum period of being under the influence is estimated to be about four hours based on a review of the experimental literature (Ramaekers et al., 2004). This time frame refers to subjective effects rather than significant measured performance deficits, which are much shorter. Typically, a peak high is experienced within 30 minutes and lasts approximately two hours Grotenhermen (2003). Studies show that after smoking cannabis, THC levels spike in blood within the first half-hour after use, then quickly decline by about 90% of this peak, with a gradual reduction thereafter. When cannabis is vapourized, the overall pattern of psychoactive effects is very similar to when smoked but more intense (Spindle et al., 2018). After eating cannabis, a peak high typically is noted between one to three hours, which typically declines to low levels within six hours. Peak highs for ingested cannabis are more delayed when ingesting versus smoking, and could be more intense than smoking, especially at larger doses.

A question of importance is what is the validity of drug tests for impairment? This is a near impossible question given that no common definition of impairment for cannabis exists. As well, although various cut-offs of concentration levels are possible, no study has been found that assessed the validity of a specific cut-off to define cannabis impairment. In the absence of proper validation, only indirect approaches are possible. One crude

approach is to compare the detection periods with blood, oral fluid and urine with the typical periods of impairment by cannabis. It is a poorer approach because it relies on averages without consideration of the variability between subjects. This approach can provide a very approximate interpretation of the validity of these biological tests to detect impairment.

As noted above, urine tests can easily be ruled out to detect cannabis impairment. These tests will not show up as positive within the first two hours after cannabis use, producing excessive false negatives for these cases. On the other hand, after two hours, the time frame for detection is excessively long, potentially lasting weeks, and the vast majority of these cases could be classified as false positive. Clearly, classification errors would be unacceptable if urine tests are used to detect cannabis impairment.

For oral fluid, the detection period is shorter than for urine, and therefore mathematically should culminate in fewer false positives, assuming that the likelihood of impairment is evenly distributed across the detection period. The detection period is much longer than the typical impairment period, and therefore this assumption can be problematic, depending on the context of the test. As described in Chapter 3, these tests detect both direct remnants of cannabis in the mouth and diffusion of THC from blood to the oral cavity only for smoked cannabis. They also are not suitable for detecting impairment because the concentration levels are dependent on two completely different phenomena. An additional shortcoming is that for ingested cannabis, the THC does not appear to diffuse into the oral cavity, and therefore only remnants can be detected. This means that for THC in pill form, the tests will have 0% sensitivity (i.e. 100% tests will be negative). Alternatively, brushing one's teeth or rinsing one's mouth when cannabis is smoked or ingested (other than in pill form) reduces these residues. For these reasons oral fluid tests have poor validity if they are being used to detect those who are a safety risk due to the acute effects of cannabis.

Overall, a relationship between OF concentrations or cut-offs and performance deficits has not been established. Yet, Australia allows their use for random OF roadside testing as a per se threshold. As pointed out by Hall and Hommel (2007), the "Australian drug testing regimes lack evidential support and was not implemented with any debate about civil liberties implications or deterrent effects."

Blood tests hold the most promise for detecting cannabis impairment. A THC reading of about 20-25 ng/mL in whole blood would provide persuasive evidence that

cannabis was smoked very recently within the last hour or so. Studies indicate that impairment is most likely in this short period after use. Concentration levels at this range suggest that cannabis was smoked, rather than ingested because THC concentration levels typically do not exceed this amount in blood when cannabis is ingested. However, if a blood test is positive at a low threshold of 2-10 ng/mL for impairment, the user may not be experiencing any effects of smoked cannabis, yet incorrectly classified. For these reasons, blood tests have poor validity for cannabis impairment.

Performance-based impairment measures

The preceding material in this Chapter shows that the acute effects of cannabis can impair performance; however, the development of a biological marker to identify those impaired has not been established. A major obstacle in the search for valid external biological measures has been that behavioural tests that measure impairment have not been established. Perhaps research should focus more on tests of behavioural measures rather than biological measures of impairment. Such a test may identify those who are not fit to drive based on their acute effects of cannabis, and possibly could be used to identify impairment from a much broader range of causes and therefore better for improving overall traffic safety.

CONCLUSION

Overall, there is scientific consensus that acute use of both alcohol and cannabis causes performance deficits that warrant prohibiting driving while impaired. Most laboratory studies find that performance deficits become substantial at a BAC level of .05%. One can conclude from existing research that after smoking cannabis, subjects remain high for at least the first hour when THC levels spike. From these observations, it appears that a THC whole blood cut-off around 20-25 ng/mL might constitute cannabis impairment for smoked cannabis. However, when cannabis is ingested, THC levels are much lower than when smoked, making blood tests of limited value when cannabis is taken orally. Existing research presented in this Chapter points toward a much higher THC cut-off in blood after smoking than currently exists in most countries with per se limits.

One major limitation of all the studies found on performance deficits and THC blood levels is that none of the studies conducted an assessment on the validity of a particular cut-off, a standard epidemiological approach outlined in Chapter 2 of this book. Hartman et al. (2015a) was the only study that attempted to calibrate their findings into meaningful criteria by calculating blood THC levels that are comparable to common thresholds from alcohol. They found 8.2 ng/mL and 13.1 ng/mL correspond to deficits from alcohol of .05% and .08% respectively, which is still higher than per se cut-offs in most countries. Data from this study and others could be re-analysed to assess validity and the likelihood that drivers at these THC levels are truly impaired. Such an assessment is needed to account for individual differences.

Although the research examined in this Chapter does show meaningful performance deficits from the acute effects of cannabis that could be considered impairment, research on a cut-off level from biological tests to detect impairment is scant. Studies on the relationship between blood tests for THC and impairment are more common than those with oral fluid testing but neither type of biological test has been shown to be sufficiently valid based on traditional epidemiological methods. None of the studies have used traditional epidemiological approaches to assess the validity of a biological cut-off level for determining impairment. Biological tests need to be assessed against a more accurate external standard of impairment in order to properly assess validity. Unfortunately, there is a gap between the recommendations for appropriate cut-offs for cannabis impairment and the experimental literature on performance deficits. It is not always evident how the effects found in laboratory studies translate into elevated crash risk on the road.

The failure of research to find a valid cut-off of any biological test and impairment has led some to extend the definition of cannabis impairment beyond the acute effects to include long-term effects, such as hangovers, withdrawal effects and cognitive deficits from long term use. Although there is empirical evidence that these issues have relevance for heavy alcohol use, comparable evidence for cannabis is not supportable by the preponderance of evidence. These issues are examined in more depth in the following Chapter.

CHAPTER 6

Long-term effects of alcohol and cannabis

HANGOVER, WITHDRAWAL & LONG-TERM EFFECTS

In this Chapter, I describe long-term effects of alcohol and cannabis, including withdrawal, hangover and lasting cognitive deficits. Legislation does not exist for the use of biological tests to assess the hangover effects of alcohol for drivers. Much of the existing and proposed legislation for cannabis worldwide set thresholds of 5 ng/mL or lower for THC in blood, which could identify substantial proportions of drivers who are not actually impaired. One rationale for low thresholds is that long-term deficits are a concern for safety on our roads. In fact, there have been studies of long-term deficits from using cannabis. In this Chapter, I compare the scientific evidence of deficits from alcohol and cannabis in terms of long-term performance deficits.

Hangover effects

Hangover effects are short-term after-effects of alcohol or drugs that occurs after the acute effects have worn off. Some authors have distinguished a difference between a hangover effect and comedown. A comedown refers to effects associated with a drug leaving the body, whereas often people refer to a hangover effect as being exclusively related to alcohol. For the purposes of this Chapter, a hangover effect refers to potential deficits from alcohol or cannabis that could occur the next day or at 24 hours after use.

The most appropriate studies for studying hangover effects are ***intervention studies*** where performance is assessed the next day or at 24 hours after cannabis use. The best studies have double-blind randomized conditions, which minimize the likelihood of bias. Randomization is the gold standard for intervention studies in terms of internal validity, allowing for the strongest conclusions about cause and effect. Double-blinding (both researcher and subjects) is recommended to reduce the likelihood of researchers or participants either knowingly or unknowingly influencing the outcomes of a study (i.e. bias). A counterbalanced design is also considered a strong research design and typically includes randomization. In counterbalanced studies, half the subjects are assigned to an experimental condition, the other half assigned to a control condition, and subjects cross-over to the other conditions, separated by an appropriate time period. Observational studies are not appropriate for this research question, as such studies have weaker research designs for drawing conclusions about cause and effect. The randomized double-blind study is the gold standard for assessing a cause and effect relationship and is the preferred research design if feasible. Since hangover effects are feasible to examine with intervention studies, these kind of studies are the focus in this Chapter.

Alcohol

Characteristics of an *alcohol hangover* include a constellation of unpleasant physical and mental symptoms, especially a headache and irritability, which occurs between eight to 16 hours after heavy drinking (Kim et al., 2003). There is some evidence of specific cognitive deficits in attention and memory during an alcohol hangover, but this may only be true for severe hangovers (Ames et al., 1997; Howland et al., 2010; Ling et al., 2010). Kim et al. (2003) reported a significant decrease in visual, memory and intellectual processes during a hangover state when compared to baseline performance, whereas Finnigan et al. (1998) found no evidence of impaired psychomotor performance. In a review of the scientific literature, Wiese et al. (2001) found that although hangovers are experienced by those with alcohol dependence, light-to-moderate drinkers incur most of the costs due to hangovers. A review of the experimental literature on hangover and performance found 27 peer-reviewed studies; only eight were judged methodologically rigorous enough to be included in the review (Stephens et al., 2008). Only two of these eight studies found performance deficits related to alcohol hangovers. However, there is evidence of measurable decrements in performance in some recent studies (McKinney et al., 2012;

Verster et al., 2014). Overall, research evidence indicates that alcohol hangovers can be associated with performance deficits, but higher-quality research is needed (Verster et al., 2010).

Cannabis

Characteristics of studies showing a hangover effect—*Hangover effects*, commonly referred to as *carry-over* or *residual effects* from single acute exposure, have been studied for cannabis. Key findings and methods are depicted in **Table 10** and summarized briefly here. The actual dosages for data in the table were converted to mg of THC if possible to allow for more accurate comparisons of use between studies.

Yesavage et al. (1985) was the first study to report carry-over effects 24 hours after smoking cannabis. It was described as a preliminary study without randomization or a placebo condition and as such, their findings should be given little weight. Also, a preliminary study by Heishman et al. (1990) should be given little weight, as it only had three subjects and no statistical tests of significance. These three studies, all with major limitations, reported long-term performance deficits from cannabis. None of the studies could adequately explain the meaning of their findings in the real world. Another study with a counterbalanced design but no researcher blinding reported effects described as subtle and of undetermined significance (Chait, 1985).

A study of airplane pilots conducted by Leirer et al. (1991) has received the most attention in terms of publicity and credibility. For these reasons, the weaknesses in the methods are described in detail here. This study has multiple methodological flaws, such as no random and blind assignment, failure to conduct a pre-test of the methods, and retention of unreliable measures (Macdonald et al., 2011), which could easily explain their findings. In terms of no random assignment to groups, the authors indicate subjects were assigned to either the cannabis or placebo condition, always referring to the cannabis condition first. If this was the true order of conditions, then the cannabis condition is confounded with practice effects (i.e. subjects do better on tasks with more experience). Instead of gold standard of randomization, the authors reported that practice effects were addressed by keeping the sessions 30 days apart. In addition, two measures (far target detection and engine malfunctions) were dropped from the analysis after data collection was complete because they were not reliably recorded. The proper procedure for a study is to decide on valid measures at the onset of the study and to keep them throughout the

study. As well, data for near target detection was kept, even though exactly the same procedures were used to collect this data as far-target detection that was deemed unreliable. Data for near-target appears unreliable based on observation of the data values at different time points. Performance scores in this study were expressed as decrements so that larger values represented greater decrements, and the marijuana condition was subtracted from the placebo condition. At .25 hours, four hours, eight hours, 24 hours and 48 hours the corresponding difference scores were 37.32, -2.46, 8.88, 49.94, and -27.63. At 24 hours, performance was worse than the most likely peak of impairment time of 15 minutes for the marijuana group (based on multiple studies). At four hours, those in the marijuana condition did better than those in the placebo condition. These data are unreliable because there is no expected trend in scores over time and findings are inconsistent with virtually all research on the acute effects of cannabis, yet these scores were included in the analyses and helped show statistical significance at 24 hours. Finally, since no blinding of researchers was conducted, researcher bias cannot be ruled out.

A study published by Dahlgren et al., (2020) also reported deficits at 12 hours of abstinence. This study is useful to illustrate why randomized double-blind studies are superior to cross-sectional designs for drawing conclusions of cause and effect. The study compared subjects abstinent from cannabis for 12 hours with non-cannabis-using healthy controls (HC) in terms of performance deficits on a driving simulator. They concluded, "Overall, cannabis users demonstrated impaired driving relative to HC participants with increased accidents, speed, and lateral movement, and reduced rule-following" (see abstract). The limitation of this kind of study is that it is challenging to select groups that are equivalent in all respects other than cannabis use. This type of limitation means that finding could be better explained by confounding variables, described in many sections of this book (see Chapter 7). In this study, the findings are highly misleading because the analysis included no adjustment for an important confounding variable (sex of subjects), where the groups were clearly not equivalent. For the control subjects only 37.5% (6/16) were males versus 82.1% (23/28) males in the cannabis group. Since the groups are highly unbalanced in terms of the proportion of males, we don't know if the findings were due to differences between groups based on sex differences between groups or cannabis use. This variable was left uncontrolled in the analyses. The authors did discover and controlled for another confounding variable, impulsiveness, and the overall findings described by the

authors disappeared. The study illustrates the challenges for addressing confounding variables with cross-sectional research designs.

Characteristics of studies not showing a hangover effect—Several other studies with stronger randomized double-blind research designs reported no hangover deficits after smoking cannabis. In a follow-up study with double-blind and randomized conditions, Chait (1990) found no carry-over effects in the cannabis condition the morning after smoking cannabis. Later, Fant et al. (1998) conducted a randomized double-blind study and concluded, "No effects were evident the day following administration, indicating that the residual effects of smoking a single marijuana cigarette are minimal" (p. 777). Curran et al. (2002) administered oral doses of THC (15 and 7.5 mg) in a well-controlled study and found no effects on about 20 different measures at 24 and 48 hours. A study by Ménétrey et al., (2005) presented figures in relation to willingness to drive at 24 hours. No statistical tests were conducted between groups at 24 hours but no effects are evident based on a visual inspection in several figures. Ronen et al. (2008) conducted a double-blind counterbalanced study and reported, "No THC-related effects were measurable 24 hours after smoking the high (17 mg) level of THC" (p. 933). The Brands et al. (2019) study is of interest because subjects were allowed to smoke cannabis at their desired level, and the cannabis group was divided into high and low THC conditions based on use. The precise amount used is unknown, but the high condition had about four times the peak level of THC blood tests than the low condition. This study also had the largest sample size of any study and used a ***between-subjects design***.

Preponderance of the evidence

The preponderance of the evidence does not point to meaningful deficits after 24 hours, yet a common myth is that the acute effects of cannabis can impair performance for 24 hours. The studies with good methodological quality did not find deficits after using cannabis at 24 hours. None of the higher-quality studies with randomized designs (Chait, 1990; Curran et al., 2002; Fant et al., 1998; Leirer et al., 1989; Ronen et al., 2008) found deficits after 24 hours. The best laboratory style studies for internal validity include double-blind randomized or counterbalanced research designs. The remaining studies that found effects did not have randomized designs (i.e. Heishman et al., 1990; Leirer et al., 1991;

Yesavage et al., 1985), were described as preliminary (Heishman et al., 1990; Yesavage et al., 1985), or had no statistical tests of significance (Heishman et al., 1990).

Table 10: *Studies of hangover effects from cannabis*

First author, year	Randomized	Double-blind	Limitations	# of subjects	Dosage	Deficits, at 24 hr or the next day
Yesavage et al., 1985	No	No	Preliminary	10	19 mg THC	Yes, 24 hrs
Leirer et al., 1989	Yes	Yes	Measures dropped	18	10 and 20 mg THC joints	No, 24 hrs
Chait et al., 1985	Yes	No	1 drop-out, only 6 subjects smoked the placebo	13	2 - 2.9% joints 90 min apart. 10 puffs	Yes, the next day
Heishman et al., 1990	No	No	Preliminary, no statistics	3	2.57% joints	Yes, the next day
Chait, 1990	Yes	Yes		12	2.1% THC joints, 40 puffs	No, the next day
Leirer et al., 1991	No	No	Measures dropped	9	20 mg THC	Yes, 24 hrs
Fant et al., 1998	Yes	Yes		10	15.6 and 25.1 mg THC joints, 8 puffs	No, the next day
Curran et al., 2002	Yes	Yes		15	7.5 and 15 mg THC capsules	No at 24 or 48 hrs
Ménétrey et al., 2005	Yes	Yes	2 drop outs, no statistics at 24 hrs	8	16.5 and 45.7 mg THC orally	No, 24 hrs
Ronen et al., 2008	Yes	Yes		14	13 mg and 17 mg THC injected in cigarettes	No, 24 hrs
Brands et al., 2019	Yes	Yes		91	93.75 mg divided into low and high groups based on usage and placebo	No, 24 hr

Despite clear methodological limitations of the Leirer et al. (1991) study, its findings have been uncritically accepted and disseminated in peer-reviewed journals. Several authors simply ignored the findings from other studies with better methods and no long-term deficits, opting to cite from the methodologically weaker Leirer et al. (1991) (Ashton, 2001; Couper & Logan, 2004; Government of Canada, 2017b; O'Kane et al., 2002; Solowji et al., 1995). O'Kane et al. (2002) went even further by improperly describing the Leirer et al. (1991) study as a ***cross-over trial***, despite the fact the authors never provided such a description. In two review articles, Ashton (1999 and 2001) uncritically accepted the findings of this study by replicating data. The aforementioned examples illustrate how myths can be propagated and maintained over time and point to the importance of adhering to standard conventions of science. The proper way to assess a research issue is to weigh the balance of the research findings in relation to the methods used.

Withdrawal effects

Alcohol

Symptoms of withdrawal effects from alcohol are dependent on the quantity and frequency of use and can range in severity from mild to severe. Difficulty sleeping, anxiety and nausea are milder symptoms, and confusion, fever, delirium, seizures, convulsions and heavy sweating are more severe symptoms.

Cannabis

Some researchers have reported withdrawal effects from cannabis, but the scientific evidence that withdrawal symptoms constitute meaningful impairment is weak. For example, Budney et al. (2001) describe withdrawal from cannabis as similar to withdrawal from nicotine. Substantial individual differences exist in terms of the nature and severity of withdrawal symptoms. Smith (2002) conducted a literature review and concluded that, "there is not a strong evidence base for the drawing of any conclusions as to the existence of a cannabis withdrawal syndrome in human users" (Smith, 2002; p. 621). In a more recent study of 469 adult cannabis smokers who made a quit attempt, 42.4% reported withdrawal symptoms (Levin et al., 2010).

Long-term cognitive deficits

Alcohol

In terms of long-term effects, evidence suggests that some long-term cognitive deficits from alcoholism can linger for up to a year (Stavro et al., 2013). Cognitive functioning and brain damage can result from extended periods of heavy alcohol use. Extreme usage can result in Korsakoff syndrome—irreversible brain damage characterized by memory loss (National Institute of Alcohol Abuse and Alcoholism, 2001). Milder deficits related to complex visual-motor functions, memory and problem solving appear possible with heavy consumption (Coambs & McAndrews, 1994).

Cannabis

Long-term cognitive deficits from long-term heavy cannabis use are possible based on studies of long-term abstinent cannabis users versus controls. The research is not conclusive due to other methodological flaws in the study designs and mixed findings. Specifically, the research is based on study designs where cannabis users who quit using (typically in controlled environments) are compared with controls. This type of research design is methodologically weak, as cannabis users may differ from non-cannabis users in many respects such as impulsiveness, risk taking, IQ, and other mental health issues. In other words, we do not know whether cannabis users were different from controls for other reasons. Therefore, it is imperative that authors of this kind of study control for potential confounding variables. Confounding variables are causally related to the outcome of interest (i.e. performance) and related to the independent variable (i.e. cannabis use). For example, an unmeasured trait such as risk-taking, IQ or age may both reduce performance and increase the likelihood of cannabis use. Therefore, any relationship found between cannabis use and performance could be spurious. In one study, Pope et al. (2002) controlled for verbal IQ when comparing total recall, long-term retrieval, and 30-minute free recall at day zero, one, seven and at 28 days of abstinence and an additional six comparisons on other test scores. The cannabis group significantly differed from the controls for only one of 18 comparisons (long-term retrieval after seven days of abstinence). This research does not show deficits of cannabis users three weeks after abstinence as most analyses conducted after abstinence showed no deficits and no significant differences for most

comparisons. The authors concluded that "…we must still live with uncertainty on the question of whether long-term cannabis use may produce cumulative neurotoxicity" (Pope et al., 2002; p.46S). Solowij et al. (2008) concluded more research, particularly brain imaging studies is needed.

In one review, Crean et al. (2011) concluded that there are decision-making and risk-taking deficits associated with long-term use. In my analysis of this review, this conclusion is not adequately derived from current scientific evidence. Specifically, Crean et al. (2011) summarize their finding as follows for different executive functions: attention/concentration – largely normal; working memory – normal; inhibition/impulsivity – mixed findings; verbal fluency – mixed findings; decision making & risk-taking – impaired. I further investigated the research they cited to arrive at the conclusion of impaired decision making and risk-taking. Only one study (Verdejo-Garcia et al., 2005) was cited to support this claim—not a sufficient number unless the quality of the study meets a gold standard in terms of methods. Crean et al. (2011) summarize the study saying cannabis users were compared to control subjects who were abstinent for 25 days and found a trend towards significance. In fact, the actual study is among 38 polysubstance abusers, who used cannabis, cocaine, heroin, MDMA and alcohol. There is no control group and no distinct group that used only cannabis. Valid conclusions of impaired decision making and risk-taking due to cannabis cannot reliably be drawn with this type of research design because cannabis use is confounded with other drug use, there is no abstinent group and the findings were not significant; in all, the methods are weak. Overall, insufficient evidence exists to draw a conclusion of long term deficits from cannabis in decision making and risk-taking, based on this literature review.

In another review of the literature, it was concluded in relation to cognitive impairments "there is no suitable evidence yet available to permit a decision as to whether long-lasting or permanent functional losses can result from chronic heavy use in adults" (Kalant, 2004; p 849). Gruber et al. (2003) found that heavy users of cannabis reported lower levels of educational attainment and income than controls. These studies have major weaknesses in research design and the magnitude of deficits found does not appear substantial. Much of the research compares cannabis users who quit with non-using controls. This is methodologically unsound, as cannabis users may differ from non-cannabis users in many respects which may be precursors to using cannabis, such as impulsiveness and mental health issues. Cannabis use may be an outcome of other individual traits. If

these deficits exist, it is not clear that they would be extreme enough to pose a meaningful safety risk while operating potentially dangerous equipment or driving a car. Not surprisingly, Broyd et al. (2016) concluded that evidence that long-term cognitive deficits persist after abstinence is weak or mixed. If cognitive deficits do exist, the magnitude of these effects not likely of clinical importance. No long term syndrome comparable to those found for alcohol has been found for cannabis.

Some additional research has been summarized on functional imaging of chronic cannabis users (Batalla et al., 2013). They concluded that cannabis use may alter brain structure but that the findings are highly variable and the studies have methodological limitations.

An article by Lovell et al. (2020a/b), albeit with limitations, is the most credible summary of the literature on long-term cognitive deficits from cannabis. In this meta-analysis, they included 30 studies of cognitive deficits related to long-term use of cannabis. Of the relevant studies found, 115 studies were excluded based on their criteria. They conclude "regular cannabis use is associated with small to moderate deficits in some cognitive domains" (Lovell et al., 2020a: p. 471).

A major limitation of this meta-analysis is how the authors dealt with the issue of confounding variables, the most important issue for cross-sectional studies in terms of drawing conclusions of cause and effect (i.e. internal validity). They recognized this limitation and concluded that "it is possible that our effect size estimates may be unreliable due to the possible presence of confounding" (Lovell et al., 2020b; p. 4). The criteria used for assessing risk of bias from confounders was whether authors identified confounders and used strategies to deal with them. Unfortunately, this approach could include studies that do not adequately address the issue of confounding. Lovell et al. (2020a) do not state the variables that should be considered confounders, and should be addressed in these studies. For example, the study by Dahlgren et al would not be excluded, even though the cannabis users were mostly males and the controls mostly females. The authors identified another confounder, risk taking, which they controlled in the analysis. Therefore, studies with faulty analysis of confounders could be included in the meta-analysis by Lovell et al. (2020a).

The big question in relation to long-term cognitive deficits is what the preponderance of the evidence means in terms of policies. Are the deficits so extreme, they provide a danger to society? Has the role of confounding variables been satisfactorily addressed? In terms of deficits, Lovell et al. (2020a) found long-term use associated with

small deficits in global cognition, learning and memory, and executive functioning and moderate deficits in decision making. No effects were found for information processing, attention, and working memory. There is no way to properly assess these findings in terms of safety risk. In terms of confounding variables, we still do not know if the relationships could be better explained by other variables, acknowledged by the authors and reviewed above. Based on these limitations, the findings of this article should not be used for policy development that includes punishment.

CONCLUSION

Preponderance of findings from studies on hangover effects indicate meaningful performance deficits from alcohol hangovers but not from cannabis. Withdrawal symptoms creating performance deficits from dependence can be mild to severe for alcohol and from mild to moderate for cannabis. Major cognitive deficits can result from long-term heavy use of alcohol but the research evidence for cognitive deficits from cannabis is weak.

CHAPTER 7

Observational studies of alcohol and cannabis risk in crashes

INTRODUCTION

An observational study, also called a field study, is a type of research study that is conducted in real-world environments. These studies and the methodological issues with them are the focus of this Chapter. They differ from laboratory studies in that researchers do not intervene or assign subjects to different conditions. Instead, substance use is detected in natural environments. Three types of observational studies in relation to crash risk of alcohol or cannabis are reviewed in this Chapter: case-control studies, ***culpability studies,*** and outcome evaluation studies.

Case-control and culpability studies are types of observational studies that seek to determine whether substance use is over-represented among crash-involved cases. In the case-control method, crash-involved drivers are compared to non-crash-involved drivers in terms of detection of substances at various thresholds. The cases and controls are ideally matched for age, sex and location of crash, and the presence of other substances. A second related approach, often used for fatal crashes, is a culpability study (also called a responsibility study) which compares individuals responsible for crashes with those who are not by examining substance-use involvement. A third approach, outcome ***evaluation studies***, is also examined in this Chapter. This type of study involves examining the impact or success of programs in achieving desired goals- for example, the impact of per se laws, intended to reduce crashes. Typically rates of crashes, ideally involving substance use, are

compared between time periods before and after the introduction of new programs. It should be noted that other types of observational studies exist, such as ***cohort*** or ***longitudinal studies***, but these are not reviewed in this Chapter. These type of studies are uncommon in accident research, and are a less efficient research design for events when outcomes such as crashes are relatively rare and the driver's substance use just before a crash is of principle interest.

Typically, the degree or magnitude of association between positive drug tests and crashes in case-control and culpability studies are assessed with ***odds ratios*** **(OR)** and sometimes ***relative risk ratios*** **(RR).** OR is used in case-control studies whereas RR is more appropriate in cohort studies. Calculation of both OR and RR start with a basic 2X2 table – the number of positive or negative tests in the two rows and the number those in crashes (or culpable) or not in the two columns. ORs are calculated by comparing two ***ratios*** whereas RRs are calculated by comparing two ***proportions.*** To calculate an OR, we use a ratio, comparing the numbers within the table, whereas for RRs, we use a proportion, which is the number divided by the row total. OR and RR are often treated as equivalent, and they do converge when both the cases and controls are representative of the larger population and the when the occurrence of crashes is rare, often stated as less than 10%. For more details regarding OR and RR, see Gordis (2014).

EPIDEMIOLOGICAL GUIDELINES FOR INTERPRETING STUDY FINDINGS

Several epidemiological criteria, in addition to transparency of methods, are used in order to interpret the validity of findings from observational studies. The main issues of importance for crash risk studies are described below.

(1) Selection bias

Bias is a systematic error in the design or conduct of study that leads to an erroneous association between drug use (i.e. more generally exposure) and crashes (i.e. more generally disease). A common source of bias in many case-control studies examining the relationship between acute effects of drugs and crashes is ***selection bias***. Findings from studies with major sources of bias should be given little weight in drawing conclusions.

A common type of selection bias is particularly severe when response rates are markedly different between the cases and controls in a study. For example, a common issue is that drug users in the control group are less likely to participate in a study than the cases, a limitation noted by Moskowitz (1985). This limitation will also have the effect of creating inflated odds ratio (OR). It is particularly problematic when consent to participate in the study is required from the control subjects but not the cases. Extreme non-response bias typically occurs in studies when fatally injured drivers, where consent is not required, are compared with living control subjects, where consent is required. In one study, were randomly selected control subjects were asked to provide a urine sample, only 49.6% consented (Brault et al., 2004; also reported by Dussault et al., 2002). Drug tests from this control group were compared to drug tests among fatally injured drivers, where no consent was needed. One could reasonably expect that a high proportion of drug users were among those who refused to participate. This means that the rate of drug use is lower in the control group than in the larger population, causing an inflated and erroneous OR.

Another common type of bias occurs when the cases are not representative of the larger population of drivers in crashes. This occurs when fatally injured drivers who are more likely than others to test positive for substances are selected for biological drug tests. This is a very common occurrence. In North America, and likely many other jurisdictions worldwide, biological tests of fatally injured drivers are not mandatory; only a subset is selected for drug tests. Bias occurs because drivers who were more likely to test positive are selected by coroners for drug tests (i.e. young men). At least a couple of studies show that drug tests were much more likely to be taken for young drivers and men in fatalities (Brault et al., 2004; Li et al., 2013). Since both men and 16–24-year-olds are more likely than others to use substances (Statistics Canada, 2012), this bias also would lead to a greater proportion of drug users (i.e. an unrepresentative sample) in the driver fatality group, and have the ultimate effect of artificially and erroneously inflating the ORs.

Culpability studies are advantageous over case-control studies of drug users because they are less likely to be biased in these ways. Culpability studies are advantageous in that typically both cases and controls are selected using the same methodology, which eliminates potential biases. I suspect it is for these reasons that, in a meta-analysis by Asbridge et al. (2012), all of the studies identified as “high quality” were culpability studies. A drawback of these studies of fatally injured drivers is the findings may not be applicable to drivers involved in non-fatal crashes.

A few studies of **non-fatal crashes** were successfully able to eliminate the likelihood of non-response bias (Brubacher et al., 2016; Brubacher et al., 2019; Drummer et al., 2020; Marquet et al., 1998; Pelissier et al., 1996). In these studies, consent to draw and test biological specimens was not required by the ethical review boards. In the studies by Marquet et al. (1998) and Pelissier et al. (1996), urine samples were obtained from hospitalized drivers in crashes and hospital controls. As noted in this book, urine is not a good biological specimen to assess safety risk. Brubacher et al. (2016) conducted a study based on excess blood taken from hospitalized subjects who required these samples for their treatment. The authors implemented anonymization procedures so that the identity of subjects could not be traced to the drug test results. The first paper by Brubacher et al. (2016) was a prevalence study and therefore findings were limited in terms of assessing crash risk related to cannabis. Two more recent case-control studies (Brubacher et al., 2019; Drummer et al., 2020) were conducted on injured hospitalized drivers where consent was not required. These later studies deserve special attention due to the reduction of selection bias in the research designs reviewed more extensively later on in this Chapter.

It should be noted that much less non-response bias exists due to non-respondents in the control groups for case-control studies of alcohol risk than cannabis risk in crashes. The main reason for this difference is that control drivers who provide a breath sample over the legal limit typically are not charged and given a ride home for their agreement to be part of a research study. Hence there is an incentive for control subjects to participate. Since these studies require police involvement to collect data from drivers, an additional factor for inebriated drivers to participate is the fear of being charged by police if they don't co-operate. Charging drivers of cannabis impairment is much more challenging as impairment cannot be detected immediately, and there are few benefits of providing a biological sample. Thus, those who use cannabis may be less likely to participate. In a recent ***case-control study*** by Blomberg et al. (2005), 97.9% of control subjects provided a breath sample, a percentage much greater than studies on other drug use. For example, in the Brault et al. (2004) study, only 49.6% of control subjects provided a urine sample.

(2) Confounding

A ***confounder*** is a variable that is causally related to a condition or serves as a proxy measure for unknown causes; it is associated with the exposure under study, but not a consequence of exposure (see Kelsey et al., 1996). In research on crashes and cannabis use, three major variables are viewed as confounders: concurrent alcohol consumption, age and sex. These variables are associated with both cannabis use and crashes. For example, males, younger people (Eustace and Wei, 2010) and those who drink and drive are more likely than others to be responsible for crashes and to drive after using cannabis. The challenge in research is to separate out the effects of cannabis from these confounders. This is typically addressed by a matching procedure in the design of a study (e.g. ensuring the same proportions of males in the cases and controls) or through statistical control of these variables in ***multivariate*** analytic procedures. When authors indicate they conducted multivariate analyses or adjusted tests, this means they have adjusted their findings to account for selected confounding variables. Epidemiologists pay particular attention to potential confounding variables and how they might influence the findings of the study, if not properly addressed. When studies report ***crude or unadjusted OR***s, this means that no consideration for any confounding variables has been included the analyses. This kind of analysis is of limited value and the finding should be treated very cautiously. If confounding variables are not taken into consideration when reporting findings, typically the ORs will be erroneously inflated.

(3) Measurement error

Measurement error, sometimes referred to as information bias, is an inaccuracy of how a phenomenon is measured and interpreted. A type of measurement error that is common in cannabis crash research is drawing conclusions about impairment of drivers based on drug tests that are invalid for this purpose. This shortcoming is compounded when different methods to measure drug use are treated as equivalent, despite ample scientific evidence that the measures are fundamentally different. Drug use can be assessed in many ways: self-reported impairment, self-reported past use, dependency, biological specimens (urine tests, blood tests, oral fluid tests), inactive metabolites (such as carboxy-THC) versus active compounds such as THC, immunoassay vs. GC/MS, and different cut-offs. Several studies have used mixed measures to examine crash risk by taking different measures for

cases than controls. For example, blood samples in experimental cases and oral fluid or urine samples in the controls are different measures. Since no valid conversion for equivalency between these measures exists, such studies should be given little to no weight when drawing conclusions of crash risk.

(4) Causation

An important objective of epidemiological studies is to determine whether relationships between variables (e.g., drug use and accidents) are causal. Causality means that a change in one variable will alter another variable. Recall that randomized experimental studies provide the strongest interpretation of causality (***internal validity***) because only one variable, the intervention, is different between the groups. For observational studies, many factors may be different between the groups and therefore, we have less confidence regarding conclusions of causality. In observational studies we are studying populations where causal factors differ among people. Therefore, we examine general causation looking at populations as a whole using probabilistic statistics, rather than single events. There are three requirements to demonstrate general causation: the suspected cause must precede the suspected effect in time, a statistical relationship between two variables of interest must exist, and the observed empirical relationship cannot be explained by a third variable. This third requirement is the most challenging to test and is related to the issue of confounding, as described above. Therefore, while an association may exist between two variables, this relationship is not necessarily causal. This is of particular importance when assessing whether substance use causes crashes. Some studies have found a relationship may exist between drug use and crashes; however, little or no efforts have been made in most studies to assess whether the observed relationships are causal. In fact, the relationship between drug users and accidents/injuries might be better explained by other confounding variables. Generally, given proper methods, the stronger the relationship, the more likely it is causal. Crude ORs with weak effect sizes, as shown in Table 11 below, should not be used to imply causal relationships.

(5) Strength of association

Another principle of epidemiology is that a strong association provides more compelling evidence of ***causation*** than a weak association. Different statistical tests are

used to measure the strength of associations, technically called ***effect sizes,*** based on how the variables are measured and on the study design. The most common tests are correlations (r) for interval or ratio level data, ORs (OR) for dichotomous variables in cross-sectional designs, and ***relative risk (RR)*** for dichotomous variables. For OR and RR values, the range of values is from 0 to infinity, with values from 0 to 1 representing a protective effect and over 1 representing a risk factor. A value of exactly 1 indicates no relationship. Some authors treat ORs and RRs as synonymous, but they are not. ORs are calculated by comparing the *ratio* of those testing positive to negative in the performance deficit group versus the same calculations in the control group. RRs are calculated by comparing the *proportion*s of those testing positive in accidents (or responsible) for all positives versus those testing negative in accidents (or responsible) for all to those testing negative. Ideally, factors such as sex, age and risk-taking propensity (confounders) should be ruled out as possible explanations for the results found, typically achieved through multivariate statistical analysis***.***

The likelihood that these tests of association could be explained by chance factors is assessed through statistical procedures, typically with confidence intervals (CI) around the ORs or ***probability values***. Studies with larger sample sizes can detect smaller differences between groups. If the confidence interval does not overlap with one or the p-value is less than .05, the association is significant. A confidence interval can be interpreted such that if the study was conducted 20 times with the exact same methods, 19 of the estimates would fall within the range. A significant probability test is a necessary condition to conclude that there is a statistical association between two variables. However, examination of the strength of the association (i.e. effect size) is also needed to conclude a relationship is meaningful. Such data can demonstrate associations, but do not show causation. Strong conclusions of causality can be drawn when findings from both experimental laboratory-style studies and observational studies converge to show the same statistical relationships. The likelihood that there is an alternative explanation for the observed effects that can be explained by confounding variables in observational studies is based partially on the magnitude ORs or RRs. I define a strong effect as an OR or RR of over 5, a moderate effect of 3 to 5, and a weak effect of between 1 and under 3 (Macdonald, 2015; p. 103). Protective effects (0 to 1) can be assessed in the same manner, as reciprocals. For example, the reciprocal of an OR of .2 is 1/.2 or 5, which is a strong effect size. A summary of the strength of relationships for different ORs is provided in **Table 11**.

Table 11: *Interpretation of effect sizes from crude ORs (OR)*

Strength of relationship	Risk factor	Protective factor
Weak	OR between 1–3	OR between .33–1
Moderate	OR between 3–5	OR between .20–.33
Strong	OR above 5	OR under .20

Cohen (1977) addressed the issue of effect sizes in a well-known book. As mentioned, a major shortcoming of probability values is they are dependent on the sample size and practically any relationship can become statistically significant with a large enough sample. Relationships with weak effect sizes are extremely common. Cohen (1977) presented guidelines for understanding whether different effect sizes could be considered meaningful based on correlational data and differences between means. More recently, Chen et al. (2010) were able to provide comparative estimates of effect sizes for ORs. They concluded that that ORs of 1.68, 3.47 and 6.71 correspond to small, medium and large effect sizes. These estimates are remarkably similar to my guidelines presented in Table 11. These guidelines provide a ballpark interpretation of the importance of effect sizes with ORs. ORs between 1-3 are extremely common, and if a crude OR, the relationship often disappears when controlling for confounding variables. Another reason that this level is not considered strong is because those above a particular cut-off limit can take often take on a wide range of values. High exposure levels may be at extreme risk but those close to the cut-off may be at no risk at all. This issue is discussed later in this Chapter where comparisons are drawn between OR point estimates and cut-offs (see Table 12).

Weak unadjusted ORs are often interrelated with other variables (i.e. confounders) that are causal. This point is illustrated in one of my studies, where I calculated ORs for a number of variables in relation to job injuries (Macdonald, 1995; Table 1, p. 706). I found 28 variables significantly ($p < .05$) related to job injuries, with ORs of 1.8 or greater and this study had a sample size of 882 participants, much smaller than each of the high-quality case-control studies (of cannabis and crashes) identified in this book. Significant independent variables in my study with without control for confounding variables included employees who feel they do too much shift work, feel their work is boring, are in conflict with others or smoke cigarettes. Importantly, crude ORs of these magnitudes can easily disappear when controlling for confounding variables and should not be interpreted as

causal (Remington et al., 2010; p. 51). By contrast, risk factors that represent strong associations and compelling evidence of causation include Blood Alcohol Content (BAC) and increased likelihood of traffic crashes (where the RRs rise exponentially to over 25 with increasing BACs), and smoking cigarettes and lung cancer (OR of 15–30, depending on dosage) (US Department of Health and Human Services, 2014).

(6) Archival data sets

Archival data is real-life data that has already been collected, typically for administrative purposes. For example, traffic records based on moving violations and crashes of automobiles is collected in every province of Canada and virtually all industrialized countries. This kind of data can be re-analysed by researchers for studies. Since the data has already been collected, these studies can be efficient in terms of low costs for data collection. However, large data sets can have enormous limitations. Selection bias, confounding, measurement error, and improper interpretation of findings are common issues with archival data. The variables collected may not be exactly what a researcher has in mind. Important types of data are often missing. For example, in epidemiological studies, control subjects (such as those not involved in crashes) are desirable but are rarely available in traffic safety data sets. Another common shortcoming of large archival databases is inconsistent methods of data collection across jurisdictions (Romano et al., 2017a). Also, how the data was collected may have extreme biases, which means conclusions drawn can be very misleading.

Datasets like the ***Fatal Accident Reporting System (FARS)*** in the U.S. and the ***Driving Under the Influence of Drugs, Alcohol and Medicines (DRUID***) (European Monitoring Centre for Drugs and Drug Addiction, 2012) databases are plagued with inconsistent data collection approaches across jurisdictions and other biases that make findings misleading. Selection bias is a major drawback with the databases on fatalities. Selection bias is evident in two ways. First, for the cases of those in crashes, data sets are incomplete as not all drivers were tested for drugs. Typically, coroners are more likely to request a drug test for those suspected of driving under the influence of alcohol or drugs, thus producing an unrepresentative group more likely to test positive. This group could be more likely to be young and male. In one study of the FARS crash data, no drug tests were conducted from 115,232 of 133,299 (86.4%) deceased drivers where this data was desired

for research purposes (Li et al., 2017). A second source of bias can occur if these drivers are compared to an external control group, as different methods are often used to collect data from control subjects (Romano et al., 2017a), previously discussed in this Chapter. Non-response bias among control subjects but not cases is another major limitation. Several studies have been published comparing FARS data with a control sample from the National Roadside Survey (NRS). This type of bias also produces elevated ORs. Yet another limitation of large data sets is that inconsistent drug testing methods are used to collect data across jurisdictions. For example, in the FARS dataset, some jurisdictions conduct blood tests whereas others conduct urine tests (Li et al., 2017).

Similar limitations have been identified by Houwing et al. (2013) for the DRUID database. Several researchers have applied a case-control methodology with this dataset and large variations in findings were found. Houwing et al. (2013) identified several sources of systematic errors in the DRUID data set, including four sources of selection bias, three sources of measurement bias and uncontrolled confounding. This well-written article is rarely cited, yet clearly points to the importance of understanding the limitations of different methods. Authors may sometimes be unaware of the limitations of their own studies, or may tend to present their studies in a favourable light, with biases that are masked in the write-up. Unfortunately, readers unfamiliar with epidemiological methods may have a biased interpretation of the preponderance of the evidence, not understanding the shortcomings in methods.

Some research has concluded that certain subgroups of drivers with BACs under .05% represent a significant crash risk. In one study, Zador et al. (2000) conducted a secondary analysis of the FARS data where BACs were taken from some fatally injured drivers, compared to those not in crashes derived from a 1996 National Roadside survey of drivers. They found that involvement in fatal single-vehicle and all fatal crashes was significantly related to drivers with BACs between .01–.019 for male drivers between 16 and 20 years old and to all drivers with BACs between .20–.49. The calculated RR for a fatal single-vehicle crash is an astonishing (unrealistic) 15,559.85 for male young drivers with BACs over .15%, over 100 times greater than estimated by Blomberg et al. (2009) for drivers at a higher cut-off of .25% alcohol. The magnitude of these effects and the differences with the data from Blomberg et al. (2009) suggest that there are substantial biases in the Zador study. A closer inspection of the methods reveals that BACs also were imputed for many drivers (estimated by the National Center for Statistics and Analysis (2017) at about 38%)

because actual BACs were not taken. ***Imputation*** is a procedure where BAC concentration levels are estimated for unknown drivers in crashes (i.e. missing data). Imputations like these create bias toward a stronger relationship than reality because BAC tests are more likely to be ordered for those suspected of drinking. In this example, 38% of the drivers had unknown BACs that were treated as valid cases based on an imputation procedure. As well, data for this study likely has considerable selection bias, where differential methods used to collect data from cases (i.e. fatally injured drivers) and controls (i.e. drivers in the general population) lead to erroneously high risk ratios. Non-response bias is a particular concern in this study. The magnitude of the risk ratios found in the Zador et al. (2000) study are much higher than others have found and the methods are biased.

WHO IS LIKELY TO DRIVE IMPAIRED—AND HOW DO THEY BEHAVE?

Two issues of importance for understanding the relationship between impaired driving and crashes and appropriate interventions, is who is likely to drive impaired and how do they behave. People who use substances have other characteristics that can increase their likelihood of crashes, such as being male or younger, which in turn are related to substance use. A challenging issue in research is separating out the importance of different risk factors from substance use in explaining the causes of crashes. The issue of confounding was described earlier in this Chapter.

Alcohol

With respect to who is likely to drink and drive, studies have consistently shown that those who are young, male or heavy drinkers are more likely to drive while impaired by alcohol and to be involved in alcohol-related crashes (Macdonald, 2003; Macdonald & Pederson, 1988). Interestingly, males and younger drivers are the two groups with an elevated likelihood of crashes without alcohol. Also, risk-taking and some personality characteristics, such as aggression, are related to an increased likelihood of crashes and likelihood of using alcohol and other drugs. These intertwined relationships make it challenging to separate whether alcohol use or some other confounders contributed to the crash.

The next question of importance is how people behave when they drive while impaired. It was noted several decades ago by Gusfield (1979) that no studies have examined how people do drive after drinking. Empirical evidence shows that some impaired drivers are able to evade detection better than others. For example, in one study those with multiple ***Driving While Impaired (DWI*)** arrests reported more risky styles of drinking and driving and more collisions than those with no arrests (Macdonald & Pederson, 1988). From this research of alcoholics (now called alcohol use disorders) in treatment, we estimated the sample drove while impaired by alcohol about 8.6 days per month, and that the likelihood of being apprehended by the police was about 1 in 1168 drinking-and-driving events. In the 1990s, it became clear that hard-core drinking drivers contributed an excessive proportion of drinking-driver crashes (Simpson & Beirness, 2004). They are characterized by alcohol problems, antisocial behaviours and worse driving records. Although Robbe and O'Hanlon (1993) and some other authors have suggested that drinkers underestimate their impairment and do not adjust their driving accordingly, this is not a correct conclusion for all drinkers. Some drivers are more likely to be apprehended and in alcohol related crashes than others. Overall, research suggests that a subset of drinkers can compensate for their impairment to some degree to reduce their likelihood of being apprehended.

Cannabis

Research similarly indicates that those younger, heavier users, and males are over-represented in cannabis-impaired driving. Again, younger people and males are more likely than older people or females to both get in crashes and to use cannabis.

Additional evidence indicates that those who experience greater negative effects from cannabis are less likely to drive under the influence than those who experience milder effects (Macdonald et al., 2008). Among clients in treatment for cannabis abuse or problems, 34.2% of people who reported driving under the influence of cannabis indicated they drove more carefully or cautiously (Macdonald et al., 2008).

Smiley (1999) reported that those who drive under the influence of cannabis may drive more cautiously than when sober. This is a common research finding. Robbe and O'Hanlon (1993) suggested cannabis users could compensate for their condition, a finding supported by Ronen et al. (2008). In another laboratory study, the authors found decreases

in average speed and a longer average distance when following cars in the cannabis conditions were found (Hartman et al., 2015b). Furthermore, a recent study also found those in those in the cannabis conditions drove significantly slower than placebos and possibly helped them avoid weaving (Brands et al., 2019). The findings from these studies are suggestive that the effects of cannabis include harm avoidance. Although some have suggested that any deviations from predictability pose a traffic safety risk, findings from these studies do not provide strong evidence that driving a little slower will enhance the likelihood of crashes. Largely unaddressed in these studies is whether the speed is so slow, it can be considered unsafe.

Although the Brands et al. (2019) study did not find weaving was affected by cannabis use 30 minutes after smoking, empirical evidence from preponderance of research evidence shows a positive relationship between weaving and THC dose (Ginsburg, 2019). Like the research on cannabis and driving speed, a threshold of when weaving becomes unsafe has not been clearly established, although Ginsburg (2019) concluded the weaving was not major. Some degree of weaving within a lane appears to be acceptable, but weaving outside of one's lane is not. I am not aware of any study where threshold of weaving is quantified as dangerous.

OBSERVATIONAL STUDIES OF CRASH RISK BASED ON THE BREATHALYZER FOR ALCOHOL AND BLOOD TESTS FOR CANNABIS

Alcohol

Borkenstein et al. (1964) conducted the Grand Rapid study on the relationship between BAC and crash risk using a case-control methodology. This landmark study found an exponential increase in crash risk with increasing BACs above .04% alcohol. Virtually every large case-control study since Borkenstein's study has shown a very strong relationship between blood alcohol content (BAC) levels and the likelihood of collisions. Relative risk curves from several studies are remarkably similar as noted by Donelson and Beirness (1985). An exponential increase in collision risk is observed in all studies when BACs

exceed .08% alcohol. Consistency of findings from different studies, as well as very strong relationships found, points to the importance of alcohol as a major cause of crashes.

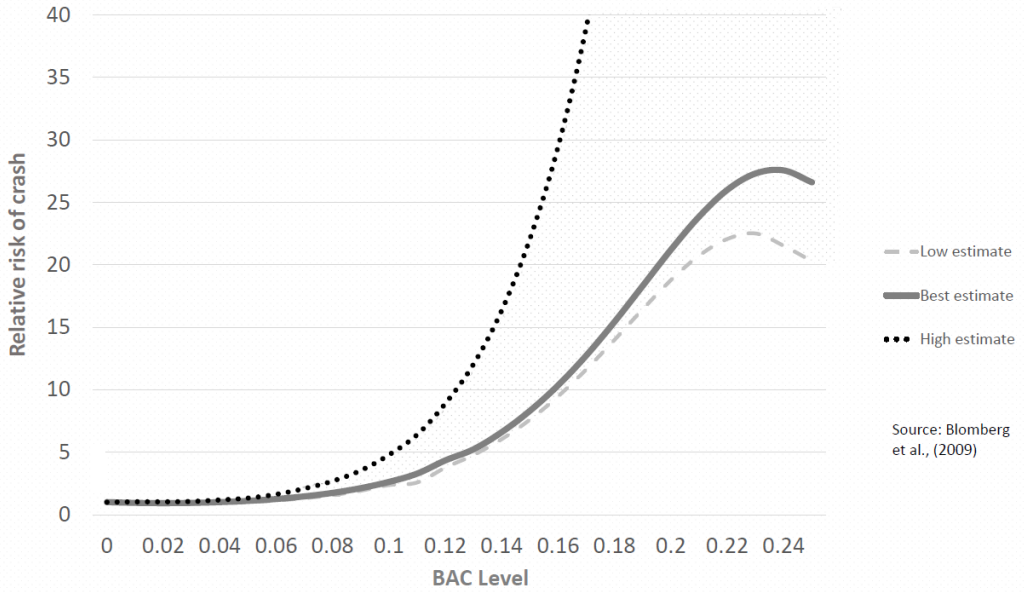
In my opinion, the best overall case-control study on BACs and crashes was conducted by Blomberg et al. (2009). This large-scale study of BAC levels among drivers included 4,919 crashes and matched controls from two American cities. Analytic epidemiological studies on alcohol impairment and collisions, such as this one, are persuasive that alcohol is a cause of collisions (see Macdonald (1997) for a summary of this evidence). Blomberg et al. (2009) presented three relative risk models: (1) an unadjusted model, (2) an adjusted model, and (3) an adjusted model where BACs of apprehended hit and run drivers were imputed. These three curves are depicted in **Figure 6,** and I have re-labeled them as (1) low estimate, (2) best estimate, and (3) high estimate. This relabeling of the curves approximates the high and low estimates of crash risk described by Donelson and Beirness (1985). The true RR curve is likely somewhere in the middle of these ranges, and is the primary basis for my re-labeling.

In the Blomberg et al. (2009) study, the model without covariates had lower RR values than the one with covariates. This conclusion is not intuitive and contrary to findings of some other studies, such as Brubacher et al. (2019) and Compton and Berning (2015). Typically, adjusted models reduce the levels of risk, not increase the risk, although a reverse relationship is still possible. The Blomberg et al. (2009) study differs from other studies in that they controlled for 33 variables (i.e. covariates), not just key confounders such as age, sex and concurrent use of substances. With so many covariates in the analysis, the reasons for this reversal cannot be easily understood. The opinion of some researchers is that it does not matter how many covariates are in a model; however, my preference is to include only those that demonstrated as confounders, such as age, sex and concurrent use of substances.

Blomberg et al. (2009) described the final adjusted RR model using an imputation procedure; however, I think the model is a high estimate for the reasons below. Imputation was used to estimate BAC concentration levels were estimated for hit and run drivers in crashes that were never caught (i.e. missing data). Specifically, BACs of drivers who left the crash scene and eventually caught were used to estimate the BACs of those who were never caught. Although, it is reasonable to assume many hit-and-run drivers who are later apprehended likely left the scene to evade detection of their drinking it is also reasonable to assume that those who successfully evaded detection (i.e. never apprehended) were

more likely to be sober than those who were caught. After all, inebriation reduces performance. If this assumption is correct, then imputation of BAC levels from those caught to those not caught will be an overestimate of RR. In the Blomberg study, this imputation procedure substantially elevated the risk of a crash at every BAC level. For example, the imputed RR for a BAC level of .25% increased from 26.60 (33 covariates) to 153.68 (33 covariates plus imputation for hit-and-run drivers)—a massive increase, especially considering the increase is due to an imputation procedure of unknown BACs among hit-and-run drivers. Overall, while this study provides concrete empirical evidence that hit-and-run drivers who are eventually caught are more likely to have been drinking than drivers who remain at the scene, the true prevalence of drinking of all hit-and-run drivers is still unknown. The prevalence of drinking is likely lower for hit-and-run drivers not caught than those caught, based on the reasons given above. I think this imputation procedure likely overstates the risk of alcohol in crashes. I think the middle curve in Figure 6 likely represents the least biased estimate of risk. However, I do believe that hit and run drivers are more likely to be impaired than those that remain at the scene. Blomberg et al. (2009) do have a valid point in this respect, but their final estimate is likely inflated. Therefore, the true estimate of risk is likely somewhere between the high estimate and the best estimate.

Figure 6: *Range of crash (responsibility) risk curves for BAC levels*



The difference between relative risk curves and cut-offs

The relative risk models (curves) presented by Blomberg et al. (2009) are derived from the curve of best fit. The curve indicates the risk of a crash at that exact BAC rather than a cut-off. These curves should not be confused with cut-off levels. I was able to estimate the unadjusted ORs[1] of crashes for several BAC cut-offs for the Blomberg et al. (2009) study from more comprehensive data (see Blomberg et al., 2005). OR calculations for different cut-offs are compared to point estimates (see **Table 12**). The ORs for cut-offs are much higher than the point estimates based on the relative risk model. For example, the unadjusted relative risk point estimate of being in a crash at .08% alcohol is 1.57 but the

[1] Adjusted ORs were not possible to calculate based on the data available. The purpose of this example is to demonstrate the difference between BAC cut-offs and those based on modeled risk curve point estimates.

OR for this cut-off is 6.6. The reason for this difference is the cut-offs represent the **average** of all case-control comparisons above the cut-off and zero BAC, whereas the modelled data represent the risk at a particular BAC point.

Table 12: *Unadjusted ORs (OR) for crashes at different BAC cut-offs compared with modelled point estimates, derived from Blomberg et al (2005) data*

BAC	Cut-off Unadjusted OR[1]	Unadjusted Point OR Estimates
Any positive BAC	1.8	
.02	2.4	.87
.04	3.4	.92
.06	4.7	1.1
.08	6.6	1.6
.10	5.7	2.4
.16	17.0	9.5
.24	24.1	21.9

Cannabis

In 1999, Bates and Blakely published a review article on cannabis and motor vehicle crashes. These authors concluded, "There is no evidence that consumption of cannabis alone increases the risk of culpability for traffic crash fatalities or injuries for which hospitalization occurs, and may reduce those risks" (Bates & Blakely, 1999; p. 231). At that time, there were three fatal injury studies on cannabis and driving, and all of them indicated a reduced risk of culpability for traffic fatalities related to a positive test. One major shortcoming of these earlier studies was drug tests were used to assess the presence of carboxy-THC, an inert metabolite of THC, and not THC. Since 1999, there have been several review papers on cannabis and crashes. A limitation of many more recent reviews is that the definitions of cannabis use were diverse. For example, several review papers did not separate the studies of blood, oral fluid tests and urine tests into groups for analyses, culminating in hybrid risk estimates, are reviewed directly below. Review papers that did separate groups are reviewed under the different biological specimens later on in this Chapter.

Review of studies with multiple measures of cannabis use

Li et al. (2012)—This study was a meta-analysis on cannabis with crash risk. They combined findings with very diverse measures of cannabis use: one study with blood tests, two studies with urine tests and five self-report studies of cannabis use (not necessarily in relation to crashes). This latter group included two studies of cannabis use in general (i.e. with an unknown connection between a crash and cannabis) and three studies of cannabis use within three hours before a crash. The combination of these studies with diverse assessment measures (i.e. ***heterogeneous***) into a meta-analysis is not appropriate and makes objective generalizations impossible. Rogeberg and Elvik (2016) also found the selection criteria from the Li et al. (2012) study hard to rationalize. Furthermore, the Li et al. (2012) study did not control for alcohol consumption or any other potential confounders, such as sex and age, in their analyses. Since these flaws are major limitations, the findings from this study are given no weight.

Els et al. (2019)—This meta-analysis also has the similar methodological limitations as the Li et al. (2012) study and should also be accordingly given no weight on conclusions about the association of crash risk from cannabis use. Specifically, this study included heterogeneous measures to assess cannabis use, including blood, oral fluid and urine tests. Four of the studies, particularly problematic, took different types of biological samples from cases and controls. No attempt was made to assess the methodological quality of the chosen studies for re-analysis. As mentioned earlier, many case-control studies have biases, which should be taken into consideration for drawing valid conclusions. Interestingly, this study largely was aimed toward understanding the safety risks of cannabis at work, yet none of the studies examined included workers.

Meta-analyses can be a useful approach to understand the magnitude of a relationship, if they are conducted properly. One very major issue with this type of re-analyses is that the study designs and measures of the original studies should be very similar to one another. A major limitation of the studies above (Els et al., 2019; Li et al., 2012) is that both the research designs and independent variables from individual studies were highly heterogeneous, making findings meaningless.

Elvik (2013)—This review article is very extensive, with 66 studies of the relationship between drugs (not just cannabis) and crash risk. This is a useful paper due to the breadth of studies found, the author's statistical approach and concern with issues of confounding and causality. The author identifies laboratory analysis of blood samples as the

most reliable indicator of recent drug use, and notes that metabolites of cannabis can remain in urine for a long time. As a result, in many studies that assessed cannabis use from urine tests, it is not clear that drugs were actually used shortly before driving. Furthermore, the author notes that estimates of risk tend to be higher in methodologically weaker studies than stronger ones. The author notes that most studies did not control well for potentially confounding factors, thus significant relationships should not be interpreted as causal. These authors estimated an OR of 1.16 for cannabis-related crashes from biological evidence (including blood, oral fluids and urine) but did not provide separate estimates for THC in blood. The low OR from this review may be related to inclusion of studies that used both more accurate blood tests and less accurate urine tests for detecting impairment. As mentioned previously, blood tests for THC concentrations are accepted as the most valid measure of impairment. Therefore, it is worthwhile to examine observational studies with blood samples that detect THC.

Gjerde et al. (2015)—This review paper was extensive, with 36 studies on cannabis. The authors also reviewed crash risk for several other types of drugs (benzodiazepines, opioids, stimulants and antidepressants). The authors do identify the type of samples used in each study but do not separate out their estimates of risk with blood tests versus other biological tests. They estimate the range in ORs for cannabis exposure and crashes between 1 and 4.

White (2017)—In this report, numerous observational studies and methodological issues related to cannabis and crash studies are examined. He concludes that the OR for cannabis and crashing is unlikely higher than 1.30 and that there is no compelling evidence of a dose-response relationship. The conclusion that there is not a well defined dose-response relationship is also described by Rogeberg & Elvik (2016) and Frith (2020).

Hostiuc et al. (2018)—The authors of this review identified 24 studies that examined the relationship between cannabis and unfavourable traffic events. They reported an OR of 1.97 for studies with blood tests, a weak effect size. However, several of the studies that used blood tests incorporated mixed measures that typically included oral fluid tests in the control subjects (for example, Gjerde et al. 2013, Li et al. 2013 and Movig et al. 2004). Mixed measures such as these create bias. The findings are uninterpretable due to the poor relationship between THC in blood and oral fluids, described in more detail in Chapter 3.

Crash risk studies of THC in blood

As mentioned in Chapter 3, blood tests for THC are currently accepted as the best biological sample for detecting likely impairment are the focus in this section. Below I first highlight three review papers aimed at understanding THC blood tests (Asbridge et al., 2012; Grotenhermen et al., 2005; Hartman et al., 2013). I then examine three higher-quality studies on the relationships between blood THC and crash risk (Brubacher et al., 2019; Drummer et al., 2004, Drummer et al., 2020). Finally, I address the issue of a dose-response relationship with an examination of a study by Laumon et al. (2005). The individual studies stand out as higher quality in terms of their study designs by minimizing bias that would distort ORs found.

Asbridge et al. (2012)—This meta-analyses study by Asbridge et al. (2012) stands out as superior to the Li et al. (2012) and Els et al. (2019) studies described in the prior section of this Chapter. The authors of this study focused more specifically on crashes where cannabis involvement was known, and emphasized studies of using THC blood tests to assess acute effects. Asbridge et al. narrowed their inclusion criteria to empirical studies of the risk of a motor vehicle collision while under the influence of cannabis (defined by self-reports of driving within three hours after use or positive THC levels from blood tests). They correctly excluded all studies with urine and oral fluid tests. An important feature of this review is that only medium and high-quality studies (based on methodological characteristics to reduce bias) were included. They assessed four studies as high quality, all culpability studies (Drummer et al., 2004; Laumon et al. 2005; Terhune et al., 1992; Terhune & Fell, 1982). Taking all the studies combined, acute cannabis consumption was associated with an increased risk of collisions compared to unimpaired drivers (OR = 1.92). Asbridge et al. (2012) noted a major bias was concurrent use of alcohol and cannabis, which, if left uncontrolled, would overestimate the effect of cannabis. To address this bias, Asbridge et al. (2012) eliminated all subjects with positive BACs from their analysis. A limitation of their review is that basic confounding variables of age and sex were not controlled for in their analyses, which means the ORs reported could be on the high side. For studies with tests of concentration of the active THC in blood samples, the ORs for a collision/culpability ranged from .82 to 4.4, with six of nine studies finding significant relationships. I see this meta-analysis as the most important contribution to our scientific understanding of the relationship between the acute effects of cannabis and crash risk/responsibility. Perhaps the greatest limitation of the Asbridge et al. (2012) meta-analysis is that age and sex,

potential confounders were not controlled. This limitation would elevate the ORs found. In order to address this limitation, Rogeberg and Elvik (2016) re-analysed the studies from Asbridge et al. (2012) and conducted a meta-analysis with 21 studies controlling for age and sex. Their analysis led to lower OR risks of below 1.5 for cannabis. In a later study, Rogeberg (2019) suggest that this OR may be on the high side based on ***Bayesian statistical modeling*** and the true OR was estimated at 1.28. Rogeberg (2019) concluded that risk estimates based on culpability studies is inflated (i.e. an ***upward bias***) compared to case-control studies.

Grotenhermen et al. (2007)—This paper is a summary of deliberations from a panel of international experts, who wrote a more comprehensive report two years earlier (Grotenhermen et al., 2005). The review was divided into laboratory studies and epidemiologic observational studies, similar to how I have presented material in this book. This group put much more emphasis on laboratory studies than observational studies in arriving at their conclusions. They concluded a per se range is likely between 3.5 and 5 ng/mL THC in whole blood. In drawing their conclusions, the authors' violated basic principles of science. Specifically, they generalized findings from studies without THC blood tests to draw conclusion on per se limits for THC in blood.

Hartman et al. (2013)—These authors reviewed epidemiological field studies that used biological tests, primarily blood tests for THC, to examine the association with crashes. However, the conclusion that THC concentrations of 2–5 ng/mL are associated with substantial driving impairment is not justifiable by the methods. First, they specifically review studies with point estimates in this THC range. Analyses by Grotenhermen et al. (2005) based on a secondary analysis of data by Drummer et al. (2004) actually shows a protective effect in this range (see **Figure 7**, below). The error in reasoning appears to be related to understanding the difference in meaning between OR cut-offs and point estimates, described in more detail above in relation to alcohol (see Table 12, above). Essentially, if low cut-offs are used, comparisons are based on the average of everyone above and below the cut-off. If there is a dose-response relationship, the OR can be misleading, including those that exhibit a protective effect as well as a risk factor. ORs based on cut-offs should not be confused with point estimates. For example, in the data from Blomberg et al. (2005), an OR for any positive alcohol test is 1.8, but point estimates are below 1 at BAC levels of .04% and below. In the review by Hartman et al. (2013), all of the studies except Drummer et al. (2004) reported very low cut-offs of 1 ng/mL or below in

blood so we cannot draw conclusions about crash risk for levels between 2–5 ng/mL from these other studies.

Drummer et al. (2004)—In this study, all the subjects were fatally injured drivers in Australia over a 10-year period (1990-1999). ORs were calculated between THC levels and crash responsibility (those responsible, n=2701; non-responsible, n=509). Drummer published some early studies where he did not find a significant relationship between culpable risk and cannabis, as cannabis positives had lower risk for culpability. As mentioned earlier, a shortcoming of these early studies is that blood tests often did not distinguish between the metabolite of carboxy-THC and THC (Bates & Blakey, 1999). In the 2004 study, Drummer specifically aimed to distinguish between crash risk for carboxy-THC and THC. He found that THC was associated with increased culpability among fatally injured drivers but carboxy-THC was not.

An increase above 1 OR begins at about 6 ng/mL THC in blood. Drummer et al. (2004) reported an OR of 6.6 at a cut-off of 5 ng/mL. Based on this model, 6 ng/mL THC could be was equivalent to .08% alcohol in terms of crash risk.

Limitations should be noted the Drummer et al. (2004) study. Only 58 drivers had positive THC samples in the Drummer study, too few to recommend a per se limit, making this curve estimate preliminary. White (2017) claims the effect sizes in the Drummer study are over-estimated. Although the authors tested for interaction effects of age and sex, these variables were not adjusted in a final model, a major limitation. Another potential shortcoming is that blood samples of THC from those deceased have not been properly validated in humans (post-mortem re-distribution). In Chapter 4, limitations of post-mortem blood tests were described. The sites in which blood are drawn and the time from death to blood extraction are critical variables that can influence to the validity THC concentrations from studies on fatally injured drivers. A particular concern is the possibility that THC concentrations in blood could increase after death, thus culminating in elevated ORs. More details are provided on this study in the next section of this book.

Brubacher et al. (2019)—In this prospective case-control study, blood samples were taken from injured drivers at trauma centres in British Columbia and analysed for drug concentration levels. Cases were derived from police crash reports to identify those responsible for the crashes (n=1178) and controls were those non-responsible (n=647). The data collection procedures minimized selection bias due to no non-respondents since the authors obtained approval for a waiver of consent. Confounders, such as concurrent

substance use, age and sex were controlled in the analyses. The results reflect THC levels obtained within a comparable timeframe that law enforcement would be able to draw blood of suspected impaired drivers (a median of 84 minutes from crash to drawing blood). This study is especially relevant to Canadian legislation because specific analyses were conducted to assess crash risk between 2-5 ng/mL THC and over 5 ng/mL THC, where drivers would be subject to criminal penalties. The OR was not significant for drivers with THC levels of 2-5 ng/mL nor over 5 ng/mL. The OR for those with a BACs exceeding .08% was significant (OR=6.0; p<.01). Hence, the impact of cannabis on crash risk was relatively small compared to alcohol.

Drummer et al. (2020) —This second study by Drummer et al. (2020) also used a culpability design that minimizes potential selection bias; however, unlike the 2004 study, the sample for this study was injured drivers, rather than fatalities. When controlling for age, sex, vehicle type and crash location in a multivariate analysis, a significant OR of 1.9 was found for THC in blood and injured drivers. For THC concentration between 1-4.9 ng/mL, and 5-9.9 ng/mL the ORs were not significant. However, significant ORs were found for over 5 ng/mL (OR=3.2) and over 10 ng/mL (OR=10). The OR of driver injury for over 5 ng/mL was substantially smaller than the same comparison in and earlier study of fatally injured drivers (Drummer et al., 2004). While speculative, the acute effects of cannabis may play a stronger role in more severe crashes involving fatalities. The median delay between the crashes and collection of blood was about two hours in this study.

Laumon et al. (2005)—This paper is of interest because it is one of the few studies to report a significant dose-response relationship between levels of cannabis in blood and culpability, claiming that their analysis confirms causality. The simplest way to test a dose-response relationship is to enter THC level as a continuous variable rather than an ordinal variable (as reported in their paper) and check for significance. Using this approach, I believe most studies would find statistical significance, yet it is unclear how Laumon et al., (2005) analysed their data in terms of dose-response. When they adjusted for confounding variables, as recommended in this book, the ORs at various THC intervals ranged from negative THC = 1, <1 THC =1.57, 1-2 THC = 1.54, 3-4 THC = 2.13, ≥ 5 THC = 2.12. These ORs do not illustrate strong dose-response relationship as odds of culpability are not increasing with each increase in THC. By contrast in this study, a very strong dose-response relationship can be observed for alcohol with adjusted ORs rising at each higher increment

from 2.7 at <.05 g/l alcohol to 39.6 CI (22.7, 68.9) at ≥ 2.0 g/l alcohol[1]. Regardless the conclusion of a dose-response relationship does not mean that those more intoxicated by cannabis are equally likely to engage in safety sensitive practices as those less intoxicated. Studies in the real world have not illustrated a strong dose-response relationship for cannabis and crashes.

Summary

Although research shows that being under the influence of cannabis is related to crash risk, this relationship is not as strong as the relationship between alcohol and crash risk. The preponderance of the evidence indicates that the odds of being in a crash or responsible for testing positive for cannabis is less than 2, a small effect size. There appears to be a moderate dose-response relationship as higher doses are related to increased crash risk, although this conclusion isn't compelling as few studies actually performed this analysis. A small dose-response relationship can be observed in the Brubacher et al. (2019) and Drummer et al. (2020) studies but not assessed statistically. Laumon et al (2005) reported a significant dose-response relationship on unadjusted data but no analysis was reported for the adjusted data. By contrast, the dose-response relationship between BAC level and crash risk is strong and compelling in practically every study.

There are several limitations of the research on crash risk in relation to THC levels. In most studies, researchers chose a low cut-off for THC, and dose-response relationships were not examined. By comparison, if researchers used a very low threshold for drinking, such as BAC positive versus negative, we would arrive at ORs of similar magnitude. I calculated a crude OR of 1.8 for crash risk for positive BACs using the detailed data from Blomberg et al. (2005). The overall OR is low likely because drivers with BACs under .04% alcohol are unlikely to be in crashes. Those with very high BACs contribute disproportionally to the OR. Yet, because a much greater proportion of the population drive under the influence of alcohol than cannabis, most studies of alcohol have found statistical significance due to high numbers of subjects, even at low cut-offs for alcohol.

[1] Note: 1 g/l =.1% alcohol

None of the above-mentioned studies proposed a cut-off value of THC in blood that might correspond to impairment. A major limitation of existing research is insufficient data to present a dose-response relationship between THC concentration levels and crash risk. Estimates of the OR for testing positive for THC and crashes are under 2, a weak effect size (see Table 11 of this book). The low ORs found in studies may be partially due to comparing THC positives versus negatives rather than choosing a higher threshold that might constitute impairment; however, studies that have examined higher THC levels have generally not found substantially higher ORs.

Comparisons of risks for alcohol (Breathalyzer) and cannabis (blood tests)

The epidemiological evidence shows that collision risk increases noticeably at .05% alcohol and increases exponentially with higher BACs, with RR estimates of at least 25 for BACs above .20%. By contrast, for crash risk related to active THC in the blood, the results from high-quality studies yield much lower risk estimates. Based on the preponderance of the evidence, an OR for a positive THC blood test and crash risk is likely under 2, and there is a weak dose-response relationship. Overall, the performance deficits from cannabis are much weaker than for alcohol. As well, the relationship between the acute effects of cannabis and crash/culpability risk is much less precise than for alcohol. The modeled curves for alcohol and cannabis are compared below.

Safety risk of high doses of alcohol and cannabis

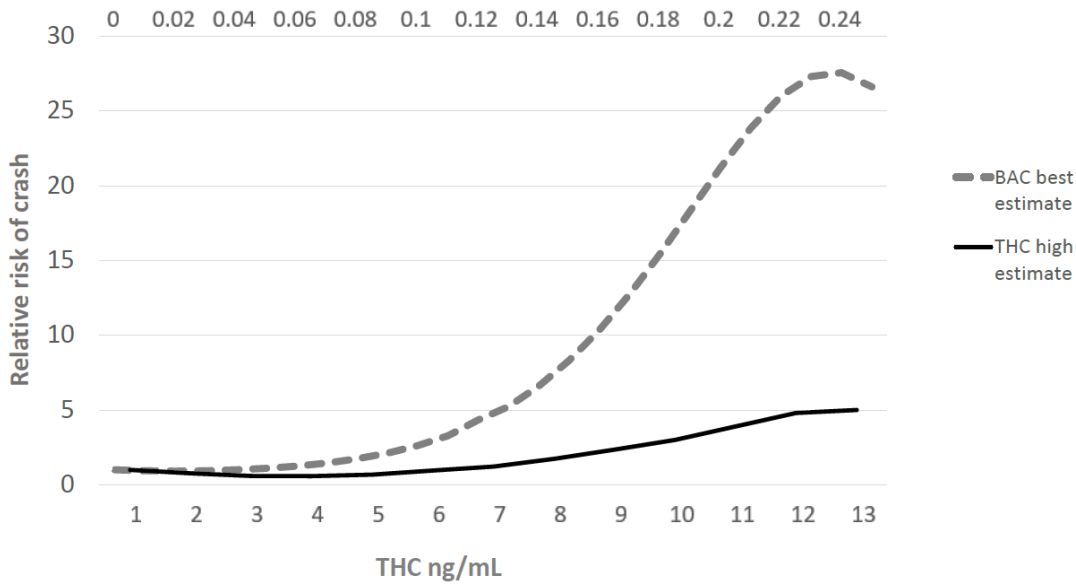
In order to compare the modeled curves, I have selected the two best studies where modeled curves were estimated. Unfortunately one study was found where the culpability risk curve for THC levels was modelled, described in the section above (Drummer et al., 2004). The OR culpability curve from the Drummer study is presented in a paper by Grotenhermen et al. (2007). Numerous studies on BAC levels and crash risk have been conducted for alcohol. In my opinion the best overall study was conducted by Blomberg et al. (2009). **Figure 7** illustrates a comparison of the modelled crash risk curves for BACs and THC levels in blood. In creating this figure, I used exact numbers of crash risk for alcohol, from Blomberg et al. (2009) and for cannabis, an estimated OR curve from a figure presented in Grotenhermen et al. (2007).

Overall, the curve risk estimate for THC is likely high, compared with alcohol for several reasons. Drummer et al. (2004) conducted a culpability study of those fatally injured whereas Blomberg did a case-control study those in non-fatal crashes. Research evidence shows BACs are more strongly related to fatal crashes than less serious crashes. If this is also true for THC and crashes, this is possible explanation of why the THC curve from Drummer's study is a high estimate. As well, the difference in research designs could create an upward risk bias for cannabis due to differences (i.e. culpability versus case-control design) (see Rogeberg & Elvik, 2016). The studies are not perfectly comparable for other reasons. Another source of bias could be due to THC being measured in deceased subjects but alcohol measured in live subjects. THC levels in blood may change after death, possibly increasing, as THC diffuses from body tissue into blood, a process known as post-mortem redistribution. Therefore, the overall THC concentration levels recorded in deceased individuals by Drummer et al. (2004) may be higher than one would expect from a case-control design with blood samples from live drivers. Finally, the ORs from the Drummer et al. (2004) study are higher estimates of the crash safety risk associated with blood THC than those found in other studies. These factors suggest the estimated risk curve from Drummer et al. (2004) is high. It is useful to directly compare the safety risk of alcohol with cannabis while understanding this possible bias.

The modelled risk curve, presented in **Figure 7** shows a high estimated THC curve in comparison to the best estimate risk curve for alcohol. Figure 7 has a double x axis in order to compare the findings of safety risk of BACs drivers versus blood THC drivers found in field studies. The THC levels refer to the lower x axis whereas the BAC levels refer to the upper x axis.

The comparison in Figure 7 indicates that the risks of crashes are greater for alcohol than cannabis taking into consideration the typical amounts of alcohol or cannabis that people consume before driving. Sewell et al. (2009) arrived at a similar conclusion. The low estimate BAC curve is substantially higher than the high estimate cannabis curve. Comparison of the models shows the risk curve becomes greater than 1 for alcohol at about .05% and at about 6 ng/mL for cannabis. This data, given all the caveats and potential biases described above illustrates that the acute effects of alcohol are far more dangerous than cannabis.

Figure 7: *Comparison of the safety risks for blood alcohol and blood THC*



BACs were also tested in the Drummer study and alcohol had a much stronger association with fatal crashes than cannabis. The conclusion that traffic crash risk for the acute effects of alcohol greatly exceeds cannabis has been found in several other studies where both alcohol and cannabis are examined in the same study. Since the same methods were used for assessing risk for cannabis and alcohol, these studies are ideal for comparative purposes of safety risks of alcohol and cannabis. In a case-control study by Laumon et al. (2005), the multivariate OR for any THC and culpability was 1.78 compared with 8.51 for alcohol. Notably in this study, several cut-offs for THC concentrations were examined. The multivariate OR for highest cut-off for cannabis, over 5 ng/mL in blood, was only 2.12 compared with an OR of 39.6 for the highest alcohol cut-off (Laumon et al., 2005; Table 3, p 4). In a study by Drummer et al. (2020) a strong adjusted fatality risk for alcohol at all concentrations was found (OR=16, $p < .05$), compared with a weak adjusted risk of THC at all concentrations (OR=1.9, ns). In a study by Longo et al. (2000; p 623) drivers who tested positive for alcohol only, were significantly more likely to be culpable for their crash compared to the drug-free group. There was no significant increase in culpability for

positive tests of THC only (Longo et al., 2000; p626, Table 1). At higher substance concentrations, Brubacher et al. (2019) found BACs>.08% were associated with an adjusted OR=6.0 (p< .0001), and a highest level of THC>= 5 ng/mL in blood had an adjusted OR=1.74 (ns). Sewell et al. (2009; p 185) published a paper comparing the effects of alcohol and cannabis on driving and concluded: "Epidemiological studies have been inconclusive regarding whether cannabis use causes an increased risk of accidents; in contrast, unanimity exists that alcohol use increases crash risk." Epidemiological research above shows the acute effects of alcohol in terms of crash risk are a much greater than cannabis.

Safety risk of low doses of alcohol and cannabis

An interesting finding of the estimates of risk of crashes/culpability from alcohol and THC is that at low levels, the curves drop (dip) below one. ORs below one are sometimes called a protective effect, but this term may be misleading since no studies have found the dips below one are statistically significant.

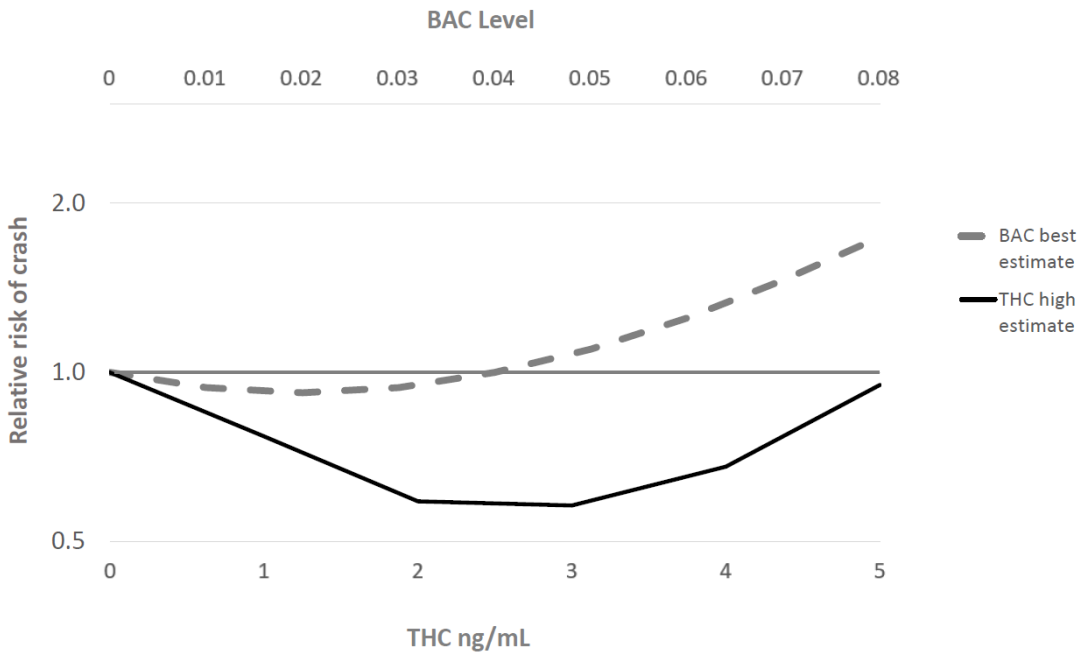
Figure 8 below shows the comparison of the two risk curves for low BACs and low THC in the blood. The dips are not visible in Figure 7 because a linear scale was used to illustrate safety risks where the values between any two points are constant. In reality the scale is logarithmic because the interval between 0-1 is equivalent to 1- infinity in terms of effect size. For example, a protective effect of .5 is equivalent in magnitude or effect size of 2 (i.e. 1/.5=2). Since the purpose of this section is to examine the effects of low alcohol and cannabis levels on safety risk, Figure 8 is presented using a more precise logarithmic scale.

As can be seen in this Figure, for both alcohol and cannabis at low levels. Both drop below one at low levels do not pose a safety risk. For alcohol, the risk at .04% or below is below one and for cannabis there is no safety risk below 5 ng/mL in blood. This figure illustrates the differences in the policy approach for alcohol and cannabis in Canada. Penalties for alcohol start at a cut-off of .08% alcohol but penalties for cannabis start at 2 ng/mL. There is much less tolerance for driving with THC in the blood than alcohol in the blood based on objective research. As well, the risks associated with drinking and driving are much greater than cannabis and driving.

Two of three models by Blomberg et al. (2009) found the risk of crashes is below one at BACs below .04% alcohol. Other case-control studies of crash risk and BACs also found a dip in crash risk at low BACs too. This phenomena was originally coined the Borkenstein dip, found in the classic 1964 case-control study. At the time was thought the

dip was unlikely to be replicated. This dip suggests a possible protective influence of alcohol at low BACs. Although this dip is not substantial or found to be statistically significant, this finding has been a source of consternation for some researchers who believe in very low BAC per se limits are justified based on safety risk. Allsop, attributed this apparent protective effect to a phenomenon called “Simpson’s paradox” (Peck et al., 2007). This situation occurs where the overall trend is the opposite in different BAC subgroups and should disappear when controlling for the confounding variables – in particular frequency of drinking. More frequent drinkers tend to be better drivers at low BAC levels. Based on Allsop’s theory, the dip is an artifact of reverse confounding. Later, Hurst et al. (1994) provided a statistical model where the dip was eliminated by controlling for frequency of drinking.

Figure 8: *Comparison of safety risks at low alcohol and cannabis levels*



Sources: Blomberg et al., (2009) and THC based on data from Drummer et al. (2004) estimated by Grotenhermen et al. (2007).

It is reasonable that those who most likely to drive under the influence of alcohol are more frequent users. As well, research suggests that frequent users are less affected by effects of alcohol than occasional users. Simply put, the effects of alcohol are not so extreme at low doses to increase safety risks for frequent users—those who are most likely to drink and drive. Although Blomberg et al. (2009) controlled for 33 variables in a second model, they did not report controlling for drinking frequency directly. A possible explanation for the dip in risk is that those who drive after one or two drinks tend to be frequent drinkers who take extra precautions while driving after drinking any alcohol, lowering their risk of crashes. As well, those who have recently used cannabis may be more frequent users who take additional precautions, thus reducing their crash risk. Regardless the magnitude of both the alcohol and cannabis dips, the effect sizes, are small. Yet, the dip certainly provides no justification that drivers at these low levels represent a meaningful crash risk.

CRASH RISK STUDIES WITH ORAL FLUID AND URINE TESTS FOR CANNABIS

Oral fluid (OF) tests

With respect to confirmatory oral fluid tests, I am only aware of one study using OF tests for both cases and controls (Compton & Berning, 2015). This study aimed to replicate the strong design features by Blomberg et al. (2009), except OF tests were taken for detection of drugs. Neither cannabis nor any other drug was significantly related to crash risk when controlling for simple demographic variables and alcohol consumption (Compton & Berning, 2015). Only BACs at or above .05% alcohol were significantly related to crashes with adjusted ORs. It should be noted that the cut-off for cannabis positive was low at 2 ng/mL in oral fluids. Although some case-control studies have used oral fluids for one group and blood tests for another group usually the cases, this approach is inaccurate as conversion factors between oral fluids and blood tests for THC are unreliable.

Urine tests

Case-control and culpability studies have been conducted comparing positive urine tests for cannabis in two groups to assess safety risk. In **Table 13** (below) characteristics of case-control with urine tests for THCCOOH (Carboxy-THC) are summarized. Overall, eight studies were found that examine the relationship between positive tests for THCCOOH in urine and crashes/fatalities. Five of these studies found no relationship, one study found a significant protective effect of cannabis and the final two studies found cannabis as a significant risk factor.

Sources of bias—In Table 13, substantial selection bias was noted in three studies, due to differential response rates among cases and controls: Brault et al. (2004), Woratanarat et al. (2009), and Del Balzo et al. (2018). Selection bias is identified in the table as either higher toward finding a positive effect and lower is toward finding a protective effect. The specific nature selection bias for the three studies identified is described in greater detail here. Brault et al. (2004) is a study based on Quebec data, which included both case-control and culpability research designs, also reported by Dussault et al. (2002). The case-control portion of the study has two sources of selection bias. The first source of selection bias is a distortion of an association that can be found in controls, due to non-participants being more likely to have used drugs than participants, since consent to testing was required for controls but not cases. In fact, only 49.6% of controls provided a urine sample. Given the choice, individuals who had recently used drugs would be less likely to agree to a drug test than those who had not recently used drugs. The existence of selection bias in this case-control component of the study is also illustrated by the authors' responsibility analysis that was free of these biases (Brault et al., 2004). Statistical significance was **not** found in the responsibility analysis. The second source of selection bias is among the cases. Brault et al., (2004), note that urine tests were much more likely to be taken for young drivers and men in fatalities. Since both men and 16–24-year-olds are more likely to use illicit drugs (including cannabis) than others (Statistics Canada, 2012), this bias would also lead to a greater proportion of drug users (i.e. an unrepresentative sample) in the driver fatality group, and have the ultimate effect of artificially inflating the ORs. An additional confounder is that those who use drugs may simply be riskier drivers. We do not know whether risk-taking or drug use is a better explanation of collision risk. The authors acknowledge these methodological limitations.

Table 13: *Characteristics of crash risk studies using tests to urine detect THCCOOH*

Author & Date	Study Type	Selection Bias and direction[1]	Lab Method	Cutoffs (ng/mL)	Variables Controlled	OR (95% CI)
Pelissier et al., 1996	Case-Control	No	Immuno - assay	50	Sex, age	1.22 (.35-4.25) **ns**
Marquet et al., 1998	Case-Control	No	GC/MS	20	Sex, age	**ns**
Woratanarat et al., 2009	Case-Control	Yes, lower	GC/MS	50	Unadjusted	0.78 (0.25-2.40) **ns**
Brault et al., 2004 also reported by Dussault et al., 2002	Case-Control	Yes, higher	GC/MS	25 screen confirmed	Age, sex, time of day/week	1.6 (1.1-2.4)
Brault et al., 2004	Culpability	No, same data as above	GC/MS	25 screen confirmed	Unadjusted	1.2 (.5-2.9) **ns**
Lowenstein & Koziol-McLain, 2001	Culpability	No	Immuno - assay	25	Age, seatbelt use, sex, time of day/week	1.1 (0.5-2.4) **ns**
Soderstrom et al., 2005	Culpability	No	ND	ND	Unadjusted	1.18 (0.84-1.64) **ns**
Del Balzo et al., 2018	Case-Control	Yes, higher	LS-MS	15 +50 screen	Those with concurrent other drugs excluded	10.88 (6.4-18.4)

ns – not significant; ND – Not described.

1. Higher is bias toward finding a positive effect and lower is toward finding a protective effect.

Selection bias is likely in the study by Del Balzo et al. (2018) due to the unrepresentative sample for the control group: professional drivers subject to mandatory urine testing. The lower likelihood of testing positive in this group likely explains the elevated OR found. Finally, the study by Woratanarat et al. (2009) may have had a downward bias as only 17% of cases agreed to participate and the percent of participating control subjects was only 53% (849 of 1605 agreed to be controls).

In addition to the studies with urine tests described above, some additional culpability studies used blood tests to detect THCCOOH. Either THC or THCCOOH can be detected with drug tests, but THCCOOH is typically tested in workplace drug testing

programs with urinalysis. Although THCCOOH has a shorter detection period in the blood than urine, it still remains in the blood for a period much longer than the acute effect (Huestis et al. 1992). Ramaekers et al. (2004, p 111, Table 1) present six crash risk culpability studies that tested for THCCOOH in blood. No significant ORs for THCCOOH were found in five of these studies and one study showed a significant protective effect.

Weighing the preponderance of the evidence, taking into consideration the quality of the research, higher quality studies have failed to find significant relationships between positive tests for THCCOOH and crash risk, and there are no credible opposing findings. Urine tests for cannabis are not valid for identifying those who represent a safety risk in traffic crashes.

Studies with mixed biological samples

Several studies of collision risk and drug detection used different biological specimens for those in collisions versus controls (Bogstrand et al., 2012; Gjerde et al., 2011; Hels et al., 2013; Li et al., 2013; Movig et al, 2004). Since the correlations between drug concentrations with different biological samples are unacceptable, this mixed measures approach introduces considerable error and bias into the findings. Therefore, these studies are not reviewed here.

EVALUATION STUDIES

Alcohol

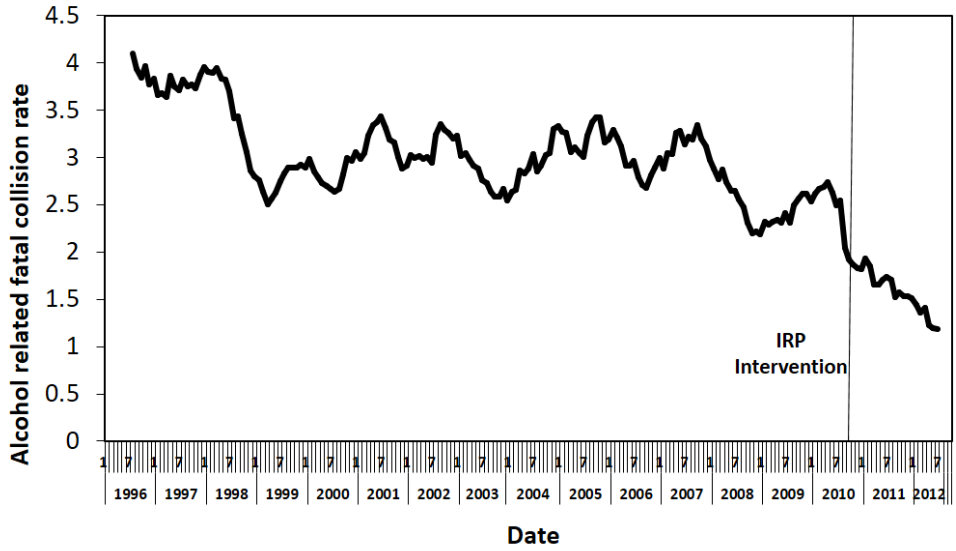
Numerous evaluation studies have assessed the impact of per se laws for alcohol (Ross, 1984; see Mann et al. (2001) for a review). There is scientific evidence that indicates very low BAC cut-offs can be effective in reducing alcohol related crashes (Mann et al., 2001). A low per se BAC threshold, such as .02% alcohol, can be beneficial in terms of reducing alcohol-related crashes since it appears to reduce drinking at the higher BAC levels.

Several studies found short-lived reductions of alcohol-related crashes after new per se laws were introduced. By contrast, a recent review article on cannabis legislation concluded that no study has been published that evaluated the impact of laws against driving under the influence of cannabis (Watson & Mann, 2016).

Per se laws are based on the principle of deterrence. The cornerstone of deterrence is punishment. According to deterrence theory, if undesirable acts are punished, then people will be less likely to engage in those behaviours. This theory is postulated to reduce the likelihood of behaviours for those caught (i.e. specific deterrence) and the larger population, who will be less likely to engage in behaviours based on the likelihood they could be punished (i.e. general deterrence). Three components of deterrence are proposed as related to effectiveness. Specifically, if the punishment is certain, swift and severe, people will be less likely to engage in those behaviours. For traffic offences, there is convincing empirical evidence that the certainty of punishment has a greater deterrent effect than increasing the severity of punishment (Wright, 2010; Nagin & Pogaesky, 2001).

In one study in BC, Canada, we evaluated a provincial law, "Immediate Roadside Prohibition (IRP)," where drivers with BACs over 0.5% received immediate impoundment of their cars (Macdonald et al., 2013). This law, aimed at providing swift intervention, showed promising positive effects at reducing three types of alcohol-related crashes. According to our analysis of traffic fatalities, the rates of fatal crashes significantly declined after introduction of the new law in 2010 (see **Figure 9**). Findings similar to these for new legislative initiatives, such as new or lower per se limits, have been reported in several other studies.

Figure 9: *Moving average monthly alcohol-related fatal collision rate per 1,000,000 licensed drivers in BC, 1996–2012*



Source: Macdonald et al., 2013

Cannabis

No evaluation studies have been published on per se laws for cannabis (Watson & Mann, 2016). According to the European Monitoring Centre for Drugs and Drug Addiction (2020) evidentiary blood tests for psychoactive substance are permitted in 23 EU member states and many of these countries have per se laws for THC. Some of these countries, such as Denmark, Ireland and Luxembourg have specified very low THC cut-off levels of 1 ng/mL. Imprisonment is a possible consequence of conviction in most countries. None of these EU countries have random testing for THC but in many countries police have the power to randomly stop drivers. Suspicion of impairment is needed to order a test. No evaluation studies are known to exist for any of these countries. To my knowledge, no evaluation studies exist on specific impaired cannabis laws on safety. The scarcity of studies is surprising, given the number of countries that have instituted deterrence style legislation for impaired driving by cannabis. Recent legalization and medical cannabis laws instituted

in some countries and U.S. states, indicates a more liberalized world, yet the lack of research on cannabis impaired driving legislation is surprising.

Some research exists that reports increases in the prevalence of cannabis in crashes over time. For example, one newspaper, *The Vancouver Sun*, indicated "drivers in fatal crashes who tested positive for marijuana without other drugs in their system tripled between 2005 and 2014 from 3.4 per cent to 12.1 per cent" after legalization of cannabis in Colorado (Fayerman; 2016). The overall thrust of the article is that legalization has created more deaths on the road. This conclusion is similar to an article published by Salomonsen-Sautel et al. (2014) that found the proportion of cannabis positive drivers increased significantly in Colorado since mid-2009, when medical marijuana became prevalent. An implication of these findings that driver fatalities increased due to cannabis is flawed. In order to conclude that greater deaths occurred, it is necessary to at minimum have a means of determining that these deaths were caused by cannabis. A greater proportion of cannabis found in drivers may be simply due to greater prevalence of use. More research has been conducted in relation to general liberalization measures. Some population-level research has been conducted on crash fatalities in relation to medical cannabis laws (Santaella-Tenorio et al., 2017). In this study, a multilevel regression analysis was performed on crash fatalities in medical marijuana and control states from 1985 to 2014. The states with medical marijuana laws had lower traffic fatality rates than non-medical marijuana states, especially among those aged 25-44 years old. The authors caution against causal interpretations of the findings and note numerous limitations of this kind of study. Most notably, the authors did not know whether drivers were under the influence of cannabis at the time of the crash.

In the U.S., a study of crash fatality rates after legalization of cannabis in Washington and Colorado was conducted (Aydelotte et al., 2017). In this study, crash fatality rates per billion miles travelled in these two states were compared to eight control states without legalization for three years before and after legalization. No significant differences were found in the states with legalization compared with the control states although significant finding were found in relation to medical cannabis. In a 5-year follow-up, Aydelotte et al. (2019) found a non-significant increase in the fatal crash rate relative to the control states in relation to legalization and a significant increase in relation to the opening of dispensaries. The selection of control states appear problematic as they were not equivalent to the cannabis states at baseline. Specifically, the control states had a

substantially higher fatal crash rate than the cannabis legalization states for every year of the study.

A sophisticated population-level study on traffic fatalities and cannabis legalization was conducted by Lane and Hall (2019). They conducted an interrupted time-series traffic fatalities, comparing the short term effects and longer-term trends of states that legalized cannabis with neighbouring states. Like other studies, they did not find that legalized cannabis was associated with long-term increases in traffic fatalities. They did report short-term increases in fatalities that also occurred in neighbouring states. In a review of the literature by Purnell and Howell (2018), the authors concluded there is no conclusive evidence concerning the risk of traffic accidents and fatalities from marijuana legalization legislation. Uruguay legalized cannabis in 2013 and Nazif-Munoz et al. (2020) reported changes in traffic fatalities in relation to legalization. They found a significant increase for light motor vehicle fatalities, but not for motorcyclist fatalities.

Some limitations of studies on liberalization of cannabis and crashes should be noted. Specifically, changes in cannabis-related crashes could not be consistently identified across jurisdictions because toxicological data collection is not uniform, making it impossible to compare findings across states for cannabis-related crashes. Therefore, in several studies, the outcome of interest was fatal crashes and we do not know whether cannabis was causally related to these crashes. As well, non-fatal crashes were excluded, as no nationwide registry exists for these events. These are major limitations of all the population level research on legalization of cannabis in the U.S. Overall, the evaluation studies of legalization policies for cannabis have not found measurable increases for crashes in relation to more liberal cannabis regulations.

The effectiveness of random versus selective breath testing

In the U.S., police must have reasonable grounds that a driver has been drinking before demanding an alcohol breath sample (a process called ***selective breath testing***). Legislation introduced in Canada on December 18th, 2018 allows for ***random breath testing*** of drivers. Random testing allows police to stop drivers at random and ask them all to provide a breath sample without any reasonable suspicion of drinking, a process also legal in Australia. Some have raised concerns that the law could be used to unfairly target visible minorities as breath tests can be ordered without suspicion (Dickson, 2018). Supporters of

this law note that a certain proportion of drivers are able to deceive police into thinking they are not over the limit and evade detection (Solomon et al., 2011). Thus, the certainty of being apprehended is increased if you are stopped by the police. As well, some people feel it is actually fairer since every driver is treated in the same fashion and no questions about prior drinking need to be asked. However, the likelihood of being caught for impaired driving will still remain low after the introduction of such legislation unless road check enforcement is increased substantially, making it unlikely that it will have a measurable long-term impact on alcohol-related arrests or crashes. Overall, empirical research has not shown that truly random breath testing will produce safer roads than selective breath testing (Elder et al., 2002; Shultz et al., 2001). In Australia where per se laws have existed for many years based on random roadside testing no known evaluation studies have been conducted (Baldock, M., & Woolley, J., 2013). Based on our knowledge of random alcohol testing, drug testing for cannabis likely has no beneficial effect above selective testing for THC, even in the hypothetical situation of a valid test.

CONCLUSION

Virtually every industrialized country has per se laws with BAC cut-offs ranging from .02% to .15%. In Canada and most U.S. states, it is a criminal offence to drive with a blood alcohol concentration (BAC) of .08%. Under federal criminal law, citizens have rights, such as the right to due process and reasonable search. Provincial governments in Canada have additional leeway to implement more stringent drinking-and-driving laws based on public health objectives. Highway and Traffic Acts in many provinces contain laws specifying lower BAC limits, commonly .05% alcohol, and immediate consequences for those who break the law. Alcohol impairment is clearly a major risk for crashes and these laws have largely been successful in reducing alcohol-related crashes. The per se laws worldwide for driving under the influence of cannabis appear to parallel those for alcohol and crashes. For impaired driving by both alcohol and cannabis, biological samples are used to convict individuals; yet the science behind alcohol and crashes differs considerably from cannabis and crashes.

In this Chapter, epidemiological case-control studies showed the relationship between alcohol and crashes is much stronger than cannabis and crashes. For alcohol, the epidemiological evidence shows strong dose-response relationship between BAC level and crash risk, increasing noticeably at .04 -.05% alcohol. By contrast, for active THC in the

blood, the dose-response relationship is weak and the magnitude of the crash risk is much weaker than for alcohol. There is some evidence that blood tests for THC at a high cut-off can be used to determine use within the past hour, a period most likely associated with safety risks and if such tests are feasible, they will likely be effective. Alcohol is much more dangerous while driving than cannabis, both in absolute terms and from a burden of disease perspective.

It is unlikely that deterrence style laws will be effective in reducing cannabis-related crashes, as found with alcohol-related crashes. There are substantial differences in the evidence base for per se laws with alcohol and cannabis. First, if the confirmatory cut-off levels for THC in blood is at or below 5 ng/mL, as they are today in most countries, the likelihood of detecting those *who are impaired* (i.e. a meaningful safety risk) is low. Therefore most drivers punished for testing positive for their use of cannabis rather than being a safety risk. The inaccuracy of the biological tests for cannabis that corresponds to a meaningful safety risk or impairment can undermine enforcement practices if not perceived as fair and just. Low thresholds mean that the laws could be challenged in courts for fairness and over time, police may become less vigilant in enforcing such laws. Although a higher cut-off with THC blood tests likely could be used to reasonably conclude impairment, a high cut-off is only feasible if blood samples are taken immediately when impairment is suspected, and only when cannabis was smoked, not ingested. An immediate blood sample appears to be unacceptable and an infringement of rights under current Canadian laws. It is even a challenge to obtain a blood sample of unconscious hospitalized drivers for alcohol analysis (Chamberlain & Solomon, 2010). Second, unlike the Breathalyzer for alcohol, no portable drug tests for cannabis exist which have the same degree of accuracy, thus reducing feasibility. Most importantly, however, research evidence has not convincingly shown that THC blood tests at cut-offs of 5 ng/mL or below indicate a reasonable likelihood of impairment.

Research has shown BAC thresholds of .02% alcohol, as exist in Scandinavians countries, do have a beneficial effect on alcohol-related crashes but there are reasons that low thresholds for cannabis will not be as effective. Even with these low alcohol limits, those caught will have consumed alcohol within a short time frame before driving or consumed a very large amount within the past day, making it relatively simple for drivers to know if they have broken the law. These low limits send a message not to drive within an hour after having a single drink or not to drive for several hours after consuming several drinks.

Although those just above the limit will have no increased risk of crashes compared to those below a low limit, those caught well above this threshold likely do represent a real safety risk. Adherence to these laws for drinkers is still relatively simple. For cannabis, the time frame in which driving must not occur under Canadian laws per se levels of 5 ng/mL could be days before the test rather than an hour or so for alcohol at .02%. Cannabis can be detected at low levels for up to several days after abstinence for daily users, and a low limit is not simple for users to understand.

CHAPTER 8

Conclusions

MYTHS AND TRUTHS

Data presented in this book shows there are many misconceptions about cannabis use, impairment and valid methods to detect impairment. I have not attempted to provide a comprehensive examination of all the issues. Rather I have focused on more major works in the field that I believe have had an impact on legal policies. In particular, I believe that policymakers are most influenced by academic papers that propose per se limits for cannabis because such a statement provides them with an empirical rationale for laws. Unfortunately, such recommendations can be flawed based on violations of science and a poor understanding of the limitations of biological tests to detect impairment. Hence myths exist. A summary of these myths and truths that I have identified in this book is provided in **Table 14**. In the sections that follow, I highlight some of these scientific studies from which these myths originated.

Table 14: *Some common myths and truths about cannabis, and how to measure impairment*

Myths	Truths
The validity of THC cut-offs in blood as an indicator of impairment has been established.	No validity studies of the relationship between THC in blood and performance, using an epidemiological approach, have been published. Therefore, no firm conclusions can be made on the accuracy of any blood THC cut-off for impairment. Higher levels of THC in blood are related to a greater likelihood of impairment.
A simple conversion factor from THC in serum or plasma can be used to estimate an individual's whole blood THC level.	Substantial variability exists between individuals of serum/plasma-to-whole blood ratios. Since this variability is large, an average plasma level cannot be used to estimate an individual's whole blood THC level.
Subjects given the same amount of THC will have similar THC concentrations at different time points.	There are substantial differences between individuals for blood, oral fluid or urine samples.
Concentration levels of THC in blood are the same as THC levels in oral fluids.	Concentration levels of THC in oral fluids greatly exceed concentration levels in blood. Oral fluid/whole blood ratio is likely between 20 and 60, with higher ratios noted shortly after use.
Oral fluid tests or urine tests are equally good as blood tests for detecting impairment.	Blood is the best biological sample to detect impairment from either cannabis or alcohol.
Oral fluids can be used to accurately identify those impaired by cannabis.	Oral fluid tests have an excessively long detection period compared with typical impairment times. Oral fluid tests only detect direct remnants when cannabis is ingested. These tests have not been shown to be good predictors of impairment.

Myths	Truths
THC concentrations in blood will be greater when cannabis is eaten than when smoked.	THC concentrations are much greater in blood within the first hour after smoking compared with the same amount eaten.
THC in is eliminated from blood at a constant rate, like alcohol.	THC is eliminated from the blood rapidly in the first hour after smoking and slowly thereafter.
Impairment and performance deficits are the same thing.	Impairment is a legal term that states performance deficits meet a particular threshold for legal penalties. Performance deficits refer to any decrement.
Immunoassay screening tests detect the same compounds as confirmatory tests using chromatography and spectrometry analysis.	Immunoassays detect several compounds with similar molecular structures, but the combination and concentration levels of each compound are unknown. Confirmatory methods are used to detect a specific compound, such as THC.
Oral fluid tests for cannabis have been validated by the Canadian police.	Oral fluid tests were pilot tested under Canadian conditions by police, and 65% of the tests were administered outside the manufacturer's suggested operating temperatures. The validity of the tests is unknown at these temperatures.
THC levels in the blood correlate closely to THC levels in the brain, similar to how alcohol content in the blood correlates with alcohol content in the brain.	Although there is a positive correlation between cannabis in the blood and brain, the relationship is weak, whereas the relationship is very strong for alcohol. A major reason for the difference is because alcohol is water soluble, whereas THC is fat soluble.
Effects of cannabis are similar for different people.	Substantial variability exists among individuals for THC levels and effects. Occasional users tend to have greater performance deficits than daily users.

Myths	Truths
The acute effects of cannabis are equally harmful as alcohol.	Research shows that alcohol is more strongly related to crash risk than cannabis at typical amounts that people use when driving.
We know how to measure impairment in laboratory situations that are at a magnitude known to be associated with crash risk.	Impairment (meaningful performance deficits) for cannabis is not well defined.
Cannabis impairment lasts 24 hours.	The preponderance of research shows cannabis impairment up to four hours after smoking and up to 10 hours from ingestion.
Cognitive deficits from cannabis can last 28 days.	There have been some studies that have drawn this conclusion but they are not definitive due to not properly controlling for confounding variables.

Origins of the myth of impairment at THC levels in blood between 3.5 and 5 ng/mL

A common myth is that THC levels at low whole blood levels below 5 ng/mL represent a safety risk equivalent to .05% alcohol. One origin of this myth is likely from a highly influential paper by Grotenhermen et al. (2007). The paper is co-authored by 11 top researchers on cannabis and performance, and published in a high impact journal, *Addiction*. The paper is well-written, transparent and provides substantial scientific language that gives the paper much authenticity. However, the authors' conclusion that 3.5 to 5 ng/mL THC in whole blood is comparable to BAC levels of .05% alcohol is not scientifically supportable because the authors drew improper generalizations. Their conclusion was drawn primarily from laboratory studies where no blood tests were conducted. An author of the paper defended this procedure as well accepted pharmacokinetic modeling that is reliable (Ramaekers, 2020). Yet, no peer reviewed citations were provided to support this claim. Research described in this book shows extremely high variability in THC blood concentrations for subjects administered the same

amount of cannabis. If variability is great, then estimates based on average have considerable error. The proper way to investigate this issue is to measure blood THC directly and assess statistical relationships between these concentrations and performance measures for each subject (Macdonald, 2020). A very common principle of research, not restricted to epidemiology, is that one should not draw inferences about the findings to a much broader population than the sample used in the study. This principle of external validity is fundamental in the social sciences (Macdonald, 2020). For this reason, and based on contradictory empirical evidence highlighted in this book, the conclusion by Grotenhermen et al. (2007) is a myth.

Researchers Hartman et al. (2013) also relied on similar laboratory studies and observational studies to arrive at the conclusion that "…recent smoking and/or blood THC concentrations of 2-5 ng/mL are associated with substantial driving impairment, particularly in occasional smokers" (Hartman et al., 2013, p. 478). These authors drew improper generalizations about blood tests and impairment. They did not cite any studies that examined THC blood levels in this range. Conclusions of impairment at these blood concentration levels should not be drawn unless the blood tests from the studies are based on this range. The reason for their conclusion may have been based on findings from some studies of significantly greater risk of crashes/culpability of cannabis-positive drivers; however, it is not proper to conclude that 2-5 ng/mL in blood represents substantial driving impairment without studies that performed blood tests.

In another laboratory study, the authors "…concluded that serum THC concentrations between 2 and 5 ng/mL establish the lower and upper range of a THC limit for impairment" (Ramaekers et al., 2006, p. 114). This range would be much lower in whole blood. They found that paired blood and performance tests from subjects were extremely low—only between 3% and 16% of the variation in blood tests were related to different performance measures. These weak relationships mean that blood tests are a poor measure of performance, yet recommendations were still made. I believe that this study also contributed to the myth that drivers with blood THC levels between 2-5 ng/mL represent a safety threat on the road.

Simply put, the studies that have asserted impairment at THC blood levels below 5 ng/mL do not conform to basic standards of science. The papers above have likely been read by legislators who do not have scientific backgrounds for understanding their flaws.

The consequence is that laws may have been implemented based on methods that do not conform to accepted scientific standards.

The main origin of the myth of 24-hour deficits from cannabis

The Government of Canada (2017b, p. 2) reports that "impairment can last for more than 24 hours after cannabis use." A report from the National Highway Traffic Safety Administration in the U.S. with expert advice from six toxicologists states that some investigators have demonstrated residual effects in specific behaviors up to 24 hours, such as complex divided-attention tasks (Couper & Logan, 2004). The World Health Organization (undated) reports "human performance on complex machinery can be impaired for as long as 24 hours" after smoking a moderate dose of cannabis.

The source of the claim of 24-hour deficits from each of these above-mentioned reports—just a few of many that exist in literature around cannabis impairment—is based on a single study by Leirer et al. (1991). The findings of this study have received an extraordinary degree of acceptance, but has multiple methodological limitations, including a failure to randomize conditions, a failure to conduct a pre-test of the methods, and retention of unreliable measures. In my opinion, this paper is not transparent, with open and clear communication, yet at the same time, it is well-written. Although as a trained epidemiologist, I was able to see these limitations, some reviewers had an inaccurate interpretation of fair conclusions from the study. No limitations of the study were mentioned, yet I found several majors flaws. As illustrated in Chapter 6, the preponderance of the evidence from studies with higher-quality methods of double-blind random assignment indicates 24-hour performance deficits from hangover effects of smoking cannabis is a myth.

The reasons for myths

There are two major issues for understanding the reasons for myths. The first is why authors conduct studies where their conclusions are not justifiable. The second issue is why so many unrecognized serious flaws are found in peer-reviewed journals. The reasons for both of these issues are related to one another and presented below. Researchers of all disciplines are expected to adhere to certain principles of science. A major principle is

transparency, or open, clear and honest communication of the research study. Unfortunately, the meaning of transparency appears to differ among researchers. Yet, it should also be noted that although flaws may exist in studies, the overall study can still be a substantive contribution to science. In this book, I have identified serious flaws in studies that invalidate the conclusions drawn by authors.

Findings from peer-reviewed journals should not be necessarily accepted as representing truth. "People have a great many fantasies about peer review, and one of the most powerful is that it is a highly objective, reliable, and consistent process" (Smith 2006; p. 179). This was the conclusion of Richard Smith, editor of the British Medical Journal (BMJ) and chief executive of the BMJ publishing group for 13 years. Articles submitted to peer-reviewed journals can be reviewed by those doing similar research in the same discipline or by those in a different discipline. The reviewers can be colleagues of the editors or unknown to the editor. Who reviews an article is dependent on a number of variables, and the likelihood of success can vary enormously depending on the reviewers. In many instances, I have found peer-reviewed publications deficient, based on standards from my discipline in epidemiology and biostatistics. Since I have an academic background, I have relied largely on publishing in peer-reviewed articles with over 130 publications. If a paper was rejected in one journal, the standard procedure was to send it for review in another journal. Rarely would the same criticism be raised twice. Thus the review process is highly variable.

There are likely several reasons for why flawed science continues to be propagated. One contributing factor in the field of substance use research is that many people have negative stereotypes or biases against cannabis users, a phenomena known as ***stigma***. Such stereotypes have been reinforced by the illegality of cannabis use and the fact that a minority of people use cannabis. The constant repetition of the negative effects of cannabis in the popularized literature of newspapers, magazines and television shapes opinions. Cannabis users commonly report stigma against them (Hathaway et al., 2011). The negative impact of stigma against substance use in healthcare recovery has been well researched (Van Boekel et al., 2013), yet the impact of stigma on research design and conclusions from studies is rarely mentioned in the academic literature. Negative stereotypes can bias how a study is conducted, and it can also affect the likelihood of acceptance of papers by reviewers.

Researchers are under pressure to produce findings that are considered worthy. This pressure can create a tendency of researchers to present their findings in a way that

others will find appealing. Worthy studies are studies with few or minor limitations. This is not what students are taught in post-graduate education. I would advise students with Masters and PhD dissertations to provide a comprehensive list of limitations of their research. In a sense, if the student shows awareness of limitations, these limitations become off limits for external reviewers to criticise. However, once students graduate and enter the real world of research, limitations acknowledged become fair game for reviewers to criticize. This especially applies when researchers are seeking competitive grant funds for research, as limitations can be mimicked by reviewers to justify rejection. Typically, the funds that will be distributed represent only a small fraction of the total funds requested. In this competitive process, reviewers tend to be very critical of applications. This process actually discourages transparency and full disclosure of research limitations and encourages selling the research. Authors attempt to persuade reviewers of the merits of their research.

As an academic, I have felt this need to publish, by both clearly stated management directives and more discreet social pressure from colleagues. Certain types of findings or conclusions, specifically those with significant results and conclusions with policy recommendations, are more likely to receive favourable reviews and be accepted for publication. These types of studies tend to be more widely read and have a greater impact. This phenomenon, known as “publication bias” is accepted as real, and can contribute to a biased representation of studies in the literature (Smith, 2006). Scholars may slice the data in ways to get significant findings and to use their study to arrive at a more concrete recommendations. This phenomena is contradictory with scientific methods.

Some researchers cut corners. I came to this conclusion early in my early career. I recall reading a scientific paper and noticed that a key reference in the paper was factually incorrect. Later on I came across several scientific articles on the same topic. I noticed that the factually incorrect reference was replicated by these additional authors. The authors of the additional papers must have simply copied the reference information into their new study without checking its veracity. Although an incorrect citation is minor, the same principles apply to more substantive issues. Instead of reading the source articles, authors might use conclusions from other researchers about a study. From a strictly pragmatic perspective, this approach is a great time saver, but the practice could culminate in myths.

Another area of concern is getting enthusiastic peer reviewers for legitimate journals. As a past assistant editor in a top-rated journal, I was responsible for finding reviewers for submissions sent to me by senior editors. I estimate that I was an assistant

editor for about 15 years with an average of about three reviews per year. Getting researchers to agree to review the papers was extremely challenging. Reviewers are volunteers. Many prospective reviewers, some who are well known in the field, would not respond to my requests, creating long delays in the process. Others would agree, but their submissions were often late and cursory. Another challenge for the review process was finding reviewers to address key disciplinary elements of a study. Since few institutions provide meaningful credit for their researchers who review manuscripts, few incentives exist to motivate researchers to participate in this largely voluntary task.

Reviewers of manuscripts submitted to journals may also be influenced by the credentials of the authors. The paper submitted by Grotenhermen et al. (2007) has an impressive list of co-authors. Reviewers could be influenced by the status of the authors and evaluate the manuscript in a favourable light or provide a more cursory review or the senior editor may want to publish it due to the status of the authors. To avoid this type of bias, some journals do not reveal the names of authors and reviewers must conduct a blind review, but most journal do not have a blind review process. A downside of blind reviews is that it is more challenging for reviewers to know whether their review is at "arm's length;" reputable journals require reviewers to declare conflict of interest and abstain from reviewing a manuscript if the reviewer has a close relationship with the authors.

The inconsistency of reviewer recommendations from high-impact journals and the influence of the credentials of authors is illustrated by a classic study by Peters and Ceci (1982). They selected 12 published articles from prestigious and highly productive American psychology departments that had been published in journals with rejection rates of 80% or more. The articles were re-submitted to the same journal 18-32 months later, under fictitious names. From a sample of 38 editors and reviewers, three (8%) journals detected the re-submission and thus halted the review process. The remaining nine articles continued through the review. Rejection recommendations were made for 8/9 of the final studies and acceptance made for only one. Clearly, the peer-review system is not perfect and each paper needs to be assessed on its own merits.

When several authors are listed on a paper, typically different aspects of the paper are delegated to individuals and often these sections are never critically assessed by others. The field of substance-use research is highly multidisciplinary, with researchers trained in sociology, psychology, history, biochemistry, law, toxicology, pharmacology and epidemiology, to name some. Papers generally do not represent a consensus where every

author has endorsed every sentence. Rather, multidisciplinary teams are created and individual team members address different aspects of a topic, typically within their discipline, and major flaws can go unnoticed. In addition, reviewers can sometimes miss important components of studies that should be revised because their backgrounds are incompatible with the authors of the papers. In this book, I have examined studies from an epidemiological perspective in the hope to help those without such training can better understand some pitfalls of research.

Guidelines for what constitutes unbiased research have been set for some types of studies. The randomized double-blind study, the gold standard of intervention research, was formulized to reduce bias for intervention studies; however, similar directives are less feasible for other types of observational studies. These studies are particularly difficult to control for confounding variables, and the issue of confounding is too often overlooked. Hence, major flaws for the interpretation of internal validity (i.e. conclusions of cause and effect) can occur.

The peer-review process does not mean that every word in every study should be accepted for fact. This conclusion is obvious, based on numerous conclusions that conflict with one another in peer-reviewed studies. The bigger question, is how to resolve the conflicting conclusions. The answer this question is apply epidemiological principles to assess the degree to which studies are valid and assess the body of knowledge through a conclusion regarding the preponderance of the evidence. Some types of research designs have better validity than other types, and the studies should be assessed in terms of the research methods to arrive at sound conclusions. The preponderance of the evidence means that conclusions should be drawn based on the body of science weighing the quality of the evidence. In this book, I have addressed several methodological issues that I think are important. In particular issues of internal validity and external validity are very important issues to consider when assessing the value of individual research. These two issues that can be overstated.

All the explanations above for myths can occur in peer-review journals. The system is far from perfect, especially when the subject matter involves stigma. For these reasons, it is best for those for laypersons to be cautious when reading studies. The methods are provided for the reader to better understand whether conclusions are justifiable.

One particular type of journal is a new threat to science. The emergence of predatory journals has exacerbated the issues described above in more recent times.

Predatory journals will typically charge a fee for publishing a paper, have little interest in ethical issues, provide minimal to no peer review and present false claims on web sites. They have little interest in scholarship, lack transparency, and use aggressive and indiscriminate solicitation practices (Grudniewicz et al., 2019). The precise definition of predatory journals has not been clearly defined, which means combating them has been challenging. It is estimated that over 10,000 journals fit this category against about an equal number that are considered legitimate. They undermine science by providing alternative opinions, often couched as science. I believe their existence has affected the quality of legitimate journals as they compete for space. Predatory journals typically have names that can easily be mistaken for reputable journals. Both researchers and readers are victims of predatory journals (Grudniewicz et al., 2019). I estimate that I get about three emails per day encouraging me to publish papers in their journals. As can be seen from the above, there are multiple reasons for major flaws in science.

TRAFFIC SAFETY

Research has shown that the acute effects of cannabis cause performance deficits that increase safety risk while driving. The question of importance is: how do we best make the roads safer? For alcohol, the answer has been to first detect impaired drivers with the Breathalyzer, then to administer sanctions against those who test above a certain threshold, typically .08% or .05% alcohol. Many feel that we should adopt similar legislative penalties for those impaired by cannabis. However, policies that do not achieve their intended purpose of identifying those who are a safety hazard can be harmful. Specifically, if the laws target cannabis users rather than those whose cannabis use is dangerous on the road, those convicted may be punished falsely. The popularity of one substance versus the other can effect decisions related to magnitude of risk. It can also affect the degree of stigma associated with use. Imagine if we only had an alcohol test that could detect if someone consumed alcohol in the past day or so who is not a safety risk at the time of the test. Would this be a test that society would endorse?

Two approaches for traffic safety

Undeniably, the automobile is viewed as an essential component of our lives, but produces substantial carnage with about 1.25 million traffic fatalities per year worldwide

and between 20 and 50 million people sustaining injuries (World Health Organization, 2015). The vast majority of these collisions, estimated at 94%, are due to human error (U.S. Department of Transportation, 2015). Clearly, driving can be dangerous and humans make many mistakes.

In order to address this safety issue related to driving, society has implemented two major approaches to address traffic safety. The first approach is based on ***harm reduction*****.** Harm reduction, a term borrowed from drug-policy initiatives, is a set of practical strategies that are aimed at reducing the negative consequences of drug use without requiring abstinence as a goal. Interestingly, the principles of harm reduction, which have been controversial in terms of drug policy, have simply been taken for granted as logical approaches for improving safety associated with driving cars. Harm-reduction approaches aim at reducing the likelihood of collisions and injuries to drivers, while accepting the fact that people drive—an activity that is inherently dangerous. Examples of harm-reduction approaches that reduce collisions include median barriers, better lighting on roads, rumble strips, removal of roadside hazards such as trees and other solid objects, speed bumps and improved traffic light switching devices. These initiatives are aimed at reducing the likelihood of crashes and associated injuries by improving the environment in which people drive. Other harm-reduction initiatives are aimed at the automobile itself. Examples of these approaches include seatbelts, daytime running lights, antilock brakes, airbags, rear-view cameras and better tires. Some of these interventions, such as seatbelts and airbags, acknowledge the possibility of collisions and are aimed at reducing the extent of injuries if collisions occur, whereas other interventions, such as daytime running lights, are intended to reduce the likelihood of crashes. Harm-reduction approaches are aimed at minimizing the likelihood and magnitude of potential harms from driving and accepts the reality that driving can be dangerous.

The second approach has been to provide rules of conduct for drivers to prevent crashes and facilitate the efficient movement of cars on the road. These rules (laws) require driver acceptance to be effective. The purpose behind many of these laws is self-evident to most people. Rules are needed to prevent chaos and traffic congestion. Traffic lights are a good example of rules that drivers must learn to facilitate safe driving. Rules are enforced by sanctions to those who disobey them. The underlying theory of sanctions is based on the principle of deterrence. According to deterrence theory, if undesirable acts are punished, then people will be less likely to engage in those behaviours in the future (i.e. specific

deterrence) and the larger population will be less likely to engage in behaviours based on fear of being punished (i.e. general deterrence). If the punishment is certain, swift and severe, then people will be less likely to engage in those behaviours. For some types of offences, including impaired driving by alcohol, there is convincing empirical evidence that increased certainty of being caught has a greater deterrent effect than the severity of punishment (Nagin and Pogaesky, 2001; National Institute of Justice, 2014; Wright, 2010).

Although deterrence has benefits in controlling human behaviour, it also has drawbacks. First, deterrence is based on the premise that humans can weigh the pros and cons of any given behaviour and refrain from behaviours that are against the law. Studies show this concept is true for some people but not others. For alcohol, those with an alcohol use disorder may see the benefits of driving under the influence more positively than others. Rational decision-making may become more difficult for this group due to substance use itself. Second, punishment or negative reinforcement in general is not the best way to control human behaviour, as punishment can cause unwanted side effects. Third, drivers make unintentional mistakes. For example, some drivers may not be aware they are breaking a law, a necessary condition for deterrence to be effective. These are some reasons that deterrence will not be fully effective among all people. Deterrence theory originated in the 18th century, and is of central importance to 20th-century criminal justice, yet empirical evidence that it works well is weak (Paternoster, 2010). It is clear that drinking-and-driving laws have saved lives, but the costs of deterrence in terms of policing and the judiciary have been steep and the public-health issue of drinking and driving remains.

Laurence Ross, who extensively researched the impact of drunk driving legislation worldwide, became skeptical about the feasibility of further reducing deaths by deterrent means due to the costs and the will to enforce such measures over time (Ross, 1984). He recommended population-level interventions such as higher taxes on alcohol (supply reduction) and a focus on safer roads/automobiles that would be beneficial for reducing the likelihood and severity of any type of collision. At the heart of these comments is a frustrating reality that humans make mistakes, not only by drinking and driving; there are many other types of mistakes that put them at risk of collisions. Deterrence-style interventions are costly and less effective than harm-reduction approaches.

The next major level of progress will only be achieved through harm-reduction initiatives that prevent humans from making mistakes. One initiative that reduces alcohol-related casualties is the ***alcohol ignition interlock*** system, where passing a Breathalyzer test

is needed to operate an automobile. The ignition interlock system, often mandated for convicted drinking drivers, is shown to be effective in reducing ***recidivism*** (Elder et al., 2011) when installed.

Being born in the industrial age and entering the information age, I have seen great changes in our world. I have seen great strides in automobile safety through technology and I have often wondered about the future of transportation. We've seen a shift in major cities from automobiles to much safer public transportation. Many years back, I envisioned an "eyealyzer," a harm-reduction approach similar to alcohol ignition interlock devices, where drivers' eyes could be analysed to determine if they are capable of driving safely. Such an instrument could serve multiple purposes. It could be used for theft control to stop people who are unauthorized to drive a particular car. Ideally, it could examine eye movements, pupil dilation and other eye characteristics for substance impairment or fatigue. The vehicle would not start for those who failed to pass. The driverless car also takes away control of potentially dangerous machinery from humans, who by our very nature are imperfect and make mistakes—albeit some make more mistakes and poorer decisions than others. Technology will eventually lead us to a safer transportation world but likely will not be perfect. However, legislative approaches that address impaired driving today rely heavily on deterrence aimed at changing human behaviour.

Laws for impaired driving

Although per se laws for alcohol impairment have been defined in practically all countries of the world, the definition of impairment varies based on cultural conditions on how to strike the balance between the rights of the individuals and perceived public safety. Low BAC cut-offs of .02% alcohol in countries such as Sweden reflect a cautious approach, where it is best to err on the side of public safety versus individual rights. Although research evidence does *not* show drivers at low BAC levels of less than .04% alcohol represent a safety issue on the road, the Swedish message is not to have even a single drink and drive within an hour, and to be completely sober before driving. The acceptability of such laws depends in part on cultural values and the severity of penalties to offenders. Fortunately, research has shown that high-severity penalties are **not** needed for effective deterrence. In any case, the Swedish cut-off does not prohibit drinking altogether—just drinking in very close proximity to driving. Those caught will have consumed alcohol within a short time

frame before driving or consumed a very large amount within the past day. The laws have the benefit of being simpler to understand than drivers calculating the amount of alcohol they can consume to stay below an impairment limit. Those over the limit will have increased risk of crashes compared to those below a low limit; however, many of those caught above a low limit may not represent a real safety risk. Some may feel that we should apply similar principles to cannabis. Unfortunately, this not possible due to the pharmacokinetics of cannabis. Low limits prohibit driving among cannabis users. The time frame for abstinence is much longer at 5 ng/mL for a THC blood test than for alcohol at .02% BAC. For daily users, this means abstinence for up to several days, and a low limit is not simple for users to understand. Nor is it clear how much cannabis is needed to reach a certain low limit; people are not always aware of the strength of the cannabis. They may share a joint with others, and therefore not know how much they used.

In North America, the legal definition of impairment for alcohol is a BAC of .08% in Canada and most U.S. states, and .05% alcohol in many Canadian provinces and some U.S. states. In Canada, the federal cut-off of .08% alcohol is consistent with severe performance deficits that virtually all people would experience. The criminal code penalty for offenders is consistent with other offences, such as criminal negligence. The lower thresholds in some provinces come with no criminal record and fewer safeguards for due process. The provincial approach is rooted more in public-safety goals. The criminal code approach is based on several intertwined purposes: deterrence, rehabilitation, protection and retribution. Overall, the bar or threshold is lower for provincial laws compared to federal ones.

Given that research shows cannabis causes impairments, an argument could be made that laws should prohibit drivers from driving even at the minimum levels of THC detection. This sends the message of zero tolerance. This argument would appear to have more merit under a criminalized system than under a regime where cannabis is legal. If cannabis is illegal, then driving with traces of cannabis in one's system could also be illegal and does not necessarily need to be based on any other purposes. However, under a legalized regime, if citizens are able to use cannabis in a safe manner, then they shouldn't be penalized. Impaired driving laws within the Criminal Code of Canada must adhere to a high standard of fairness and be considered reasonable. This fairness means that laws should not be discriminatory. Discrimination is the incorrect labelling of an individual based on perceived group characteristics. In this case, the per se laws for cannabis impairment

identify users of cannabis who may not be a safety risk on the road, not those impaired by cannabis while driving. As well, individuals charged for offences should have the right to defend themselves (i.e. due process). Laws that do not achieve this purpose undermine the system itself and can create disrespect by citizens against the justice system. Examples of this disrespect occurred during the prohibition laws against alcohol in the early 1900s and those against cannabis making possession illegal. The truth is that research does not demonstrate impairment for the majority of individuals at levels of 5 ng/mL or below and this fact could lead to challenges against such laws. In this book, comparisons are drawn between current legislation for impaired driving by alcohol.

Canadian laws for cannabis-impaired driving

With legalization of cannabis in Canada, concerns have been raised regarding driving under the influence of cannabis. The federal government has recommended two-tiered criminal laws with a per se blood THC range of 2–5 ng/mL and a cut-off of 5 ng/mL to address cannabis-impaired driving. These laws are similar to those in many other countries in that they have legislation prohibiting driving at cut-offs of 5 ng/mL or below. However, I am not aware of any country that has laws against the range of 2–5 ng/mL. In order to charge a driver under the act, the police must have reasonable suspicion to believe they are under the influence, which could include an oral fluid screening test. Drivers who test positive from an oral fluid screening test will be subject to additional diagnostic tests aimed at determining impairment. These tests could include a DRE assessment or a blood test to detect THC concentration levels. Neither of these approaches have been properly validated. DRE laws have been criticized for being cumbersome requiring costly training of officers, subject to errors and can be challenged in court. However, the consecutive stages of assessment reduce the likelihood of false positives (Gordis, 2014). The per se blood limit passed by the Canadian government offers a more streamlined approach but may be subject to even greater inaccuracy.

A shortcoming of the new Canadian legislation is the use of oral fluid tests. The Drager 5000 point-of-collection oral fluid test is authorized for police to use as a screening test. The cut-off for the test will be 25 ng/mL. This number may seem high but it is not. First, the test is based on an immunoassay procedure. Recall that screening tests of this type cannot distinguish THC from other compounds of a similar molecular structure, such as

carboxy-THC or hydroxy-THC. This means that the cut-off of 25 ng/mL includes a combination of these different cannabinoids, not simply THC. Second, 1 ng of THC in whole blood is estimated about equivalent of possibly 20 to 60 ng for a confirmatory oral fluid. This cut-off is low compared to a blood sample. There are other reasons to question the use of oral fluid tests in Canada. Oral fluid tests were pilot tested under Canadian conditions by police, and 65% of the tests were administered outside the manufacturer's suggested operating temperatures. The validity of the tests is unknown at these temperatures. Several police forces, including the Vancouver police, have already stated they will not be using the tests for these and other reasons (CBC News, 2018).

Cannabis is a risk-aversive drug. In other words, those who are feeling the effects of cannabis may compensate in ways that make their driving safer. This could include actions such as driving more defensively by slowing down and leaving more distance when driving behind a car. Although research indicates occasional users are more adversely affected by cannabis, this group is less likely to drive after use than regular users. Laboratory studies have also yet to demonstrate that drivers who are daily users don't represent a meaningful safety risk.

Higher cut-offs than 5 ng/mL in blood will be related to higher likelihood of impairment. Data from the Drummer et al. (2004) study (reported in Grotenhermen et al., 2007) is suggestive that a cut-off in the range of 6–8 ng/mL is equivalent to about .05% alcohol and Hartman et al. (2015b) study found that 8 ng/mL THC in whole blood is equivalent to .05% alcohol. These two empirical studies provide some evidence that a cut-off in the range of 6–8 ng/mL could be used as an impairment threshold possibly equivalent to the safety risk at .05% alcohol; however, even this conclusion is highly tentative based on sparse research. Again, concentration levels of THC in the blood from ingested cannabis are quite different than when smoked and this aforementioned conclusion is based more on smoked cannabis than ingested.

The Canadian laws for cannabis-impaired driving are more streamlined than the DRE process but not perfect. The procedures to obtain blood and then to analyse it have not been well specified. Since THC is not eliminated in blood at a constant rate, blood samples must be obtained at the time of suspected impairment, which likely is impractical. Also, since confirmatory tests using chromatography and spectrometry methods are needed for accurate assessment of THC concentrations but require time-consuming laboratory methods, it is not clear how analyses will be carried out in a timely manner. Most

of the conclusions made in this book were known when the new Canadian laws were established. A major issue is that the validity of blood tests at the levels proposed has not been scientifically proven.

Although the DRE approach has limitations, it has strengths against per se laws for driving while impaired by cannabis. The main strength is that the DRE approach focusses more on behavioural criteria related to being under the influence of cannabis rather than criteria based on low blood THC thresholds. Clearly, legislation that makes our roads safer is a good thing. However, the rationale behind penalizing drivers within a low range of 2-5 ng/mL THC is dubious, as this range has not been clearly demonstrated in any laboratory study as meaningfully related to crash risk. Papers that support per se legislation at these low thresholds are not rooted in traditional principles of scientific inquiry. It is inconceivable from an evidence-based perspective that such legislation will make our roads measurably safer. Legislation that has little scientific basis to improve traffic safety has the potential to do more harm than good.

Higher THC levels in blood might be used to draw more valid conclusions of impairment for those who smoked cannabis, but more research is needed. Research suggests an average individual who tests positive at 10 to 20 ng/mL THC would have likely smoked cannabis within the hour, which might be a suitable measure of impairment when cannabis is smoked. However, if cannabis was ingested or if the individual tested was a daily user, this cut-off will not meet common scientific standards of validity. As well, there is suggestive evidence that testing for both THC and hydroxy-THC may provide a more valid indication of impairment when cannabis is ingested.

As mentioned previously, the decision on where to set the threshold for impairment for per se laws depends in part on trade-offs between sensitivity and specificity. There are several other issues to consider. First, what are the safety risks and what are the expected benefits and drawbacks? These benefits will depend on the nature of the laws, including fairness of the laws, severity of the penalties, and simplicity for citizens to adhere to the laws. These factors should be taken into consideration when choosing to implement per se laws and appropriate cut-off.

In terms of safety risks of alcohol, studies also have clearly demonstrated that high BAC levels cause severe performance deficits associated with safety risks based on laboratory and observational studies. Evaluation studies show per se laws at any cut-off (i.e. .02% alcohol or more) can reduce traffic crashes and associated injuries and fatalities. For

cannabis, laboratory studies have shown moderate performance deficits within an hour after smoking and a few hours after ingestion. Observational studies have found a weak relationship between the acute effects of cannabis and crashes. There is no credible evidence from evaluation studies that per se laws for cannabis reduce traffic crashes. Overall, there is a convergence of evidence that alcohol is a major risk factor for crashes. For cannabis, there is evidence that the acute effects represent a moderate safety risk in comparison to alcohol based on laboratory and observational studies. No credible evidence exists that per se laws will be effective, based on evaluation studies.

Major differences exist between cannabis and alcohol. Alcohol is much more widely used than cannabis. Research indicates that at the quantities generally used by populations, driving under the influence of cannabis is less dangerous than alcohol. The pharmacokinetics of alcohol cannot be applied to cannabis. Alcohol is a simple, water-soluble drug, resulting in blood concentration levels which correspond very closely to performance levels. THC is fat-soluble, meaning it tends to bind closely to fat cells. THC concentration levels in the blood only correlate well with performance deficits within an hour after use when smoked, but not ingested. Alcohol is eliminated from the body at a constant rate, whereas THC is variable at different points in time. Furthermore, the extended elimination process of THC from the body is much slower than for alcohol. THC levels can remain above 5 ng/mL in blood several days after use, among for daily users (Desrosiers et al., 2014a). For these reasons, concentration levels below 5 ng/mL THC provides a poor correspondence to impairment. Finally, extreme variability exists for THC concentrations among individuals who consume the same amount of cannabis. The exact reasons for this variability is complex, depending on frequency of use, route of consumption (i.e. smoked or ingested) and factors unknown. By contrast, variability among BAC levels among individuals is directly dependent on a few known factors, including body weight, sex and age. These differences are challenges for identifying cannabis impairment from drug tests. Our success with detection of impairment for alcohol and interventions have created an illusion that cannabis-impaired driving can be addressed in the same manner as alcohol-impaired driving.

In terms of detection methods, the Breathalyzer is simple to administer, non-intrusive, provides results in a timely manner and BAC readings correlate closely with performance deficits. Validity studies have been conducted to identify optimal cut-offs for impairment, taking into consideration the trade-off between sensitivity and specificity.

Blood tests for THC are considered the best biological specimen to assess impairment. Yet, these tests are intrusive, require training to take blood, and analyses need to be conducted in laboratory settings with possible delayed findings and have a major flaw of not being accurate measures of performance deficits at common per se levels. These impediments create insurmountable roadblocks for implementing cannabis per se laws that have comparable validity to those for alcohol.

Severity of penalties should be related to the fairness of the laws and expected benefits. Impaired driving by alcohol is addressed through both criminal and provincial laws. Criminal per se laws are based on breath samples of over .08% alcohol with a summary conviction resulting in a criminal record, possible jail time and fines. The severity of these consequences is severe. Per se laws also exist under the provinces, typically at a .05% cut-off and penalties such as car impoundment, driving restrictions and fines. The penalties are less severe than under the Criminal Code of Canada and the cut-offs lower. Laws can be implemented within traffic-safety codes of provinces that may unfair to some individuals, but are best for protecting public health at large, especially if the consequences of getting caught are not overly severe. Fines for speeding are an example of this principle. Not all drivers who are caught driving over the speed limit are necessarily a traffic-safety risk, but lower speed limits overall do save lives. The provincial laws are justified from a public-health perspective. For cannabis, a blood test between 2-5 ng/mL results is a summary conviction (less severe) and a blood test over 5 ng/mL results in an indictable conviction (more severe). Both types of convictions result in criminal records.

Another consideration of per se laws is how easily can people understand and comply with the laws. For alcohol, higher BACs of .05% and over are involve each person determining how much they can drink and stay under the limit. This involves a public education. Typically, an average man (175 pounds) who has two or less drinks on an occasion will be under a limit of .05% alcohol. Alcohol is eliminated from the body fairly quickly at a constant rate, and the level of alcohol in the blood is highly related to performance. Cannabis, however, is eliminated from the blood very slowly at a variable rate and the level of THC in the blood is poorly related to performance (with the possible exception of very high concentration levels). This fact makes it difficult for users to understand and comply with per se laws, such as those in Canada, as users could test positive without any form of performance deficits and the length of time they must abstain from use can be extremely long – days, not hours as exists for alcohol.

LIMITATIONS AND DIRECTIONS FOR FUTURE RESEARCH

A major theme throughout this book is greater adoption of the epidemiological method for assessing the validity of biological tests for impairment. The acute effects of cannabis do cause performance deficits that can meet standards of impairment, but how to measure them has been elusive.

One major issue of importance that is rarely discussed: *How do we define impairment?* Impairment implies defining a specific threshold where performance deficits are considered severe enough to warrant sanctions. More research is needed on defining the magnitude of performance deficits in laboratory conditions that constitute impairment. As well, more research should go into establishing the criteria for impaired performance after taking cannabis, building on progress by the working group led by Kay and Logan (2011). Another approach to defining impairment is by drawing on the studies of alcohol deficits at different BACs and using these performance deficits to calibrate equivalent thresholds for cannabis Hartman et al. (2015b).

Once these performance criteria that define impairment have been established, epidemiological validity studies can be conducted to determine optimal biological cut-offs that best detect these impairment thresholds. To achieve this goal, the validity of the tests for specific thresholds should be assessed using the epidemiological methods described in Chapter 2. People will disagree on the optimal trade-off between sensitivity and specificity; however, with scientific data at least the proportion of false negatives and false positives will be known. Presently, the state of our knowledge on these issues for any cut-off remains poor, and cut-offs are guesswork based on the wrong kind of studies. Only with this knowledge on the validity of drug tests can legislators adopt evidence-based policies and provide a rationale for them.

A misleading aspect of many studies is an emphasis on measures of central tendency at the expense of measures of dispersion (i.e. variability). Such studies may give the impression of similarity among people; however, statistics on variability are needed to draw such conclusions. Not a single study was found that used an epidemiological approach to validate any cut-off level (for a possible per se limit), an approach that incorporates individual variability of THC cut-offs in relation to impairment. Substantial variations exist between individuals in the absorption and elimination of THC at different time points, yet often summary statistics of central tendency are used to describe the relationship, giving

the impression of a high degree of similarity between people. Another example is the assertion that an average serum/plasma blood THC concentration can be used to estimate an individual's whole blood THC level based on an average ratio between the two. This assumption does not take into consideration the fact there is substantial variability between individuals for this ratio, and the ratio can change considerably for a given individual at different points in time. Therefore, any estimates based on a conversion factor will have a high degree of error for a given individual.

Greater distinction and understanding by researchers needs to be made between effect sizes and probability values. Probability values are based on the sample size and the dispersion of the variables and indicate the likelihood that a relationship is due to chance. Effect sizes refer to the actual strength of statistical relationships. Statistical significance (i.e. $p<.05$) is best thought of as necessary but not sufficient to conclude a relationship is meaningful. If a statistical test is not significant, then there is no point in looking at the strength of a relationship. In this book, I have defined effect sizes that I consider weak, moderate or strong based on different levels of measurement. The degree to which the magnitude of an effect size is considered appropriate depends on the purpose of the relationship. Numerous other epidemiological research issues were raised in this book, illustrating how failure to adhere to standard research protocols can culminate in erroneous findings. Issues such as bias, confounding, measurement error, effect sizes and the difference between correlation and causation were highlighted.

One issue that creates challenges for interpreting, comparing and integrating findings is the diverse ways in which cannabis research is carried out. Although some diversity in research designs is good for science, lack of standardization of how researchers' conceptualized importance constructs is a particular problem in cannabis research. Greater standardization is recommended in relation to several areas of cannabis research as follows:

1. Researchers should quantify the amount of cannabis administered more consistently in laboratory studies. A particular concern was from studies that only reported the THC content but not the weight of the product, which meant that the actual THC consumed was unknown. The best way to define the amount consumed is by expressing the dosage in terms of mg of THC.
2. Another issue that made it difficult to compare findings of studies is the high proportion of research studies that analysed THC in serum or plasma, yet in

North America the legal standard is whole blood. As pointed out in this book, although some researchers claim near constant serum/plasma-to-whole blood THC ratios, research shows the ratio between the two is too variable to adopt a universal conversion ratio. THC concentration levels in serum and plasma can be considered equivalent. Overall, the use of whole blood is the best medium to analyse THC for practical legislative purposes. Research should more consistently use whole blood for analyses.

3. Some studies reported use of screening drug tests whereas others reported more accurate confirmation drug tests with chromatographic and spectrometry methods. All studies should use confirmation methods, unless a specific rationale is given, such as convenience of administration, and inaccuracies associated with screening tests are stated as a limitation.
4. Much more research is needed on oral fluid tests before being used in legal situations. Particularly concerning is that when cannabis is ingested (as opposed to smoked) oral fluid tests cannot identify prior use of any kind, unless cannabis residues are left in the mouth. Oral fluid tests have no sensitivity for detecting ingested cannabis, other than direct remnants left in the mouth.

In addition to the above, there should be universal acceptance that urine tests should not be used to detect impairment. Although this conclusion appears well accepted in the traffic-safety world, it is still contentious among some in Canada who support urinalysis for employees. Five observational studies were reviewed that found no significant relationship between positive urine tests for cannabis and crashes.

More research is needed on the validity of oral fluid *confirmation* tests. Research shows ingested cannabis cannot be detected with oral fluid tests, unless remnants are left behind—a very major shortcoming. This means that if THC is ingested in pill form or if users brush their teeth after use, they could be impaired but have a negative test. Currently, laws that penalize drivers based on oral fluid confirmation tests are not evidence-based on safety risk.

Another issue of uncertainty is the role of hydroxy-THC in performance deficits. Hydroxy-THC is a psychoactive metabolite created by the body's breakdown of THC that is redistributed in the bloodstream and is created to a much greater extent when cannabis is ingested versus smoked. We need to learn more about the differences between smoked

and ingested cannabis in terms of performance deficits. Comparisons of studies by Hunault et al. (2014), where subjects smoked cannabis, and Ménétrey et al. (2005), where subject ingested cannabis, longer durations of effects for ingested cannabis were found yet much lower concentration levels of THC in the blood. More research is needed on how these compounds are related to detection periods and cut-offs for smoked versus ingested cannabis.

Observational studies that used biological tests (whether blood, oral fluids or urine) to assess the relationship between crashes and cannabis typically chose extremely low cut-offs of compounds such as THC. This approach is surprising, given that drug concentrations can be measured as a continuous variable and choosing to divide the data into two arbitrary groups reduces the likelihood of finding statistical significance. The strength of the relationships (i.e. effect sizes) were very low in most studies, with ORs typically under 2 and many studies failed to find statistical significance. If the drug concentrations are analysed as a continuous variable in relation to crashes, the likelihood of statistical significance is increased because this measure is more precise. As well, such data could be used to propose an evidence based cut-off for impairment. White (2017) maintains a dose-response relationship has not been convincingly shown in research. Greater doses of ingested cannabis do appear to be related to greater performance deficits.

CONCLUSION

In this book, I have compared our knowledge of the effects of alcohol and cannabis in relation to driving and Canadian legislation to reduce driving casualties. The safety benefits of the Breathalyzer for detecting alcohol impairment are substantial and undeniable. A large body of credible research shows alcohol negatively affects performance in a dose-response relationship and the BAC level from breath tests is an excellent measure of performance deficits. As well, alcohol is eliminated from the body at a constant rate and is water-soluble, which means there is a close relationship between alcohol in the blood and performance. Although alcohol can cause long-term effects, such as those due to hangovers, the Breathalyzer cannot detect such deficits.

For cannabis detection, the story is much different. Blood tests, considered the most valid biological sample, are inconvenient, difficult to administer in a timely fashion and have poor relationships between low levels of THC and performance deficits. Based on the

preponderance of research, a THC range between 2 and 5 ng/mL and a cut-off and above 5 ng/mL for impairment are very low compared to the alcohol cut-offs at .05%. As well, the theory of 24-hour impairment is best described as a myth and does not provide an evidence-based rationale for adopting low THC cut-off levels. The preponderance of research evidence shows cannabis hangovers are not meaningfully related to performance deficits. A very conservative lower per se impairment cut-off is 6 ng/mL and can be justified based on one empirical observational study, and 8 ng/mL based on one laboratory study as equivalent to .05% alcohol. These studies have not been replicated or validated. No credible evidence of meaningful impairment below 5 ng/mL exists for smoked cannabis.

Some readers may be surprised at some of the findings in this book, yet many of the conclusions I have drawn are not original. There is growing agreement that the detection of THC in blood is associated with ORs between 1 and 2, a weak effect size. In fact, many of my findings were also independently found by special task forces. For example, in Canada a Task Force (McLellan et al., 2016) aimed at studying the implications of cannabis legalization arrived at conclusions below that are consistent with those of this book:

- Cannabis-impaired driving is more complex to study than alcohol-impaired driving;
- Whereas evidence was gathered over many years to arrive at an established metric for alcohol intoxication - Blood Alcohol Concentration (BAC) - these types of data do not exist for cannabis; While scientists agree that THC impairs driving performance, the level of THC in bodily fluids cannot be used to reliably indicate the degree of impairment or crash risk;
- Other challenges exist, including the need to account for the rapid and sharp decline of THC levels in the blood in the hours following consumption through smoking (with edibles the decline is more gradual).

Furthermore, Peterson et al. (2019) concluded:

- Research studies have been unable to consistently correlate levels of marijuana consumption, or THC in a person's body, and levels of impairment. Thus some researchers, and the National Highway Traffic Safety Administration, have observed that using a measure of THC as evidence of a driver's impairment is not supported by scientific evidence to date.

- The body metabolizes marijuana differently from alcohol. The level of THC (the psychoactive ingredient of marijuana) in the body drops quickly within an hour after usage, yet traces of THC (non-psychoactive metabolites) can still be found in the body weeks after usage of marijuana.
- The National Transportation Safety Board has advised that "about 2 alcoholic drinks" within an hour will cause a 160-pound male to experience decline in visual functions and in the ability to perform two tasks at the same time. Based on current knowledge and enforcement capabilities, it is not possible to articulate a similarly simple level or rate of marijuana consumption and a corresponding effect on driving ability.
- Several factors complicate the effort to determine what, if any, impact marijuana usage has on the likelihood of being involved in a crash. Chief among these factors is the distinction between correlation (things that occur together) and causation (one thing that causes another thing).

In this book, the applicability of biological drug tests to detect a meaningful safety risk from cannabis use were reviewed. Each of the main types of biological drug tests—blood, oral fluids and urine—were poor for detecting safety risks due to cannabis. As well, although the safety risk for cannabis use can be meaningful, they are minor in comparison to alcohol. These findings suggest that interventions to prevent cannabis-impaired driving are warranted. Since the drug tests by themselves are not viable in terms of valid conclusions, we are left with identifying some other criteria to identify safety risks related to cannabis. Other types of behavioural tests are possible. Unfortunately, our present knowledge of these tests also indicates they are not valid. The question of importance is, what can be done that is reasonable? Certainly, legislation prohibiting drivers from using cannabis while driving seems reasonable. As well, if drivers exhibit major behavioural symptoms of performance deficits, intervention is warranted.

In terms of safety issues related to drivers, we know that distracted driving is unsafe. The root causes of distracted driving are when attention is divided between driving tasks and other activities. Smoking, eating and drinking non-alcoholic beverages while driving increase safety risk. Yet, these are issues that could be easily addressed with legislation. Manufacturers of cars are permitted to install cup holders and ash trays in automobiles. Fast food take-out restaurants are permitted on major highways. These are

likely safety issues that appear to be endorsed in our society, and legislation could easily be enacted to prohibit these encouragements, but political will to act is weak. Our priorities need to shift from beliefs of what should be done to empirical research of what is unsafe and where feasible, enacting equitable policies to address safety risks related to driving.

An issue described in this book is how we choose our priorities for improving safety. I believe perceptions on how to address cannabis and driving stem largely from our knowledge of alcohol and driving. Clearly, alcohol is a menace on the roads, and the Breathalyzer has been useful as a deterrent in preventing fatalities, injuries and crashes. Since alcohol has been legal in most countries but cannabis is not, many people may think that cannabis must be worse than alcohol, yet this is not true. As shown in this book, many of the lessons we have found from alcohol and driving cannot be applied to cannabis and driving.

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Glossary

Absolute alcohol— The percentage of pure alcohol (i.e ethanol) in an alcoholic beverage

Absolute harms—For this book, absolute harms refer to safety risks of alcohol and cannabis without consideration that the prevalence of alcohol is much greater than cannabis.

Absolute standard— The specific criteria needed to be considered safe.

Accuracy— Accuracy refers to the ability of a diagnostic test to correctly classify people as impaired or not impaired, assuming a given definition of impairment. It is calculated by the proportion of true positives and negatives divided by all the cases being examined.

Different indicators of validity of a biological test for impairment

	Impaired	**Not impaired**
Test: Positive	True positive	False positive
Test: Negative	False negative	True negative

Alcohol ignition interlock—An ignition interlock system is a Breathalyzer installed in a vehicle where a driver must provide a negative breath sample (under a prescribed threshold) in order to start the automobile.

Back-extrapolation—Extrapolation is an estimation of a value based on extending a known sequence of values beyond the area that is observed. Back extrapolations involve estimating values at a prior point in time.

Bayesian statistical modeling— A theory in statistics where probability is influenced by the degree of belief in an event.

Between-subjects design—A type of experimental design where each subject is assigned to only one condition (such as a cannabis or placebo condition).

Bias—A systematic error in the design or conduct of a study that leads to an erroneous association between the exposure and an outcome, such as crashes.

Blinded study/double-blinded study—A study in which subjects do not know what treatment they are receiving (participant blinding) or where the experimenters do not know what treatment the subjects are receiving (experimenter blinding). In a **double-blind** study, neither the participants nor the experimenters know who is receiving a particular treatment.

Blood Alcohol Content (BAC)—The percentage of alcohol in the bloodstream.

Cannabidiol (CBD)—A non-psychoactive compound from cannabis which is reported to have medicinal properties.

Cannabinoids— Compounds in the cannabis plant that are structurally related to THC.

Carboxy-THC (THCCOOH)—A metabolite in THC that is typically detected with urinalysis and used to identify drug users rather than those impaired. Like THC, carboxy-THC can be stored in fat cells for days, and possibly weeks in heavy daily users.

Case-control study—A study that compares subjects (i.e. cases) who have a disease or condition (i.e. traffic crashes are considered a condition) to those without a condition (controls), in terms of exposure to a risk factor (e.g. alcohol or cannabis). The purpose is to determine the relationship between the risk factor and the condition through calculations of ORs.

Causation (general causation)—Causality means that a change in one variable will alter another variable. General causation can be determined for groups of people using epidemiological methods. There are three requirements in order to demonstrate general causation in epidemiological studies: the suspected cause must precede the suspected effect in time, a statistical relationship between two variables of interest must exist, and the observed empirical relationship cannot be explained by a third variable.

Central tendency—A statistical measure that describes the way in which a group of data clusters around a central value. There are three measures of central tendency: the mean, the median and the mode.

Chromatography and spectrometry—Gas chromatography mass spectrometry (GC/MS) is an instrumental technique, comprising of a gas chromatograph (GC) coupled to a mass spectrometer (MS), by which compounds can be quantified. A combination of these methods is considered the gold standard and referred to as confirmatory tests.

Coefficient of determination (r^2)—A squared correlation coefficient (r) which can be interpreted as the percent of variation in one variable that is shared with a second variable.

Coefficient of variation (CV)—This is the ratio of the standard deviation to the mean of a sample. The CV is useful to compare the dispersion (variability) among variables that have different units of analysis and means. Variability is standardized whereby sample distributions with different units of analysis can be compared directly in terms of their variability. Low CVs indicate low variability.

Cognitive— The process of thinking or mental processes, such as learning things.

Cohort study—A group of people followed-up over time assess the risk of developing a particular health outcome.

Compound—A substance composed of atoms from more than one element, held together by chemical bonds.

Confidence interval (CI)—A range that means that if the sample was drawn with exactly the same methods, the sample characteristics would lie within this range about 19 out of 20 times.

Confounder—A confounding variable is causally related to a condition or serves as a proxy measure for unknown causes and is associated with the exposure under study but is not a consequence of exposure (see Kelsey et al., 1996).

Continuous variable —A variable that can have many values.

Controlled dosing studies—Studies in which subjects are administered substances, and concentration levels with drug tests are measured at different time intervals after use.

Conversion factors—A conversion factor is defined as a ratio of two numbers that make them equivalent.

Correlation—The extent to which two variables are statistically related to one another.

Correlation coefficient (r)—A statistical measure of the degree to which changes of the values of one variable are related to changes of the values of another variable. The value of r can range from -1 to +1, with the sign indicating the direction of the relationship. A correlation of r=1 is perfect and 0 is no relationship (see also *Coefficient of determination*).

Correlation of determination (r^2) – The percentage of variation in one variable that can be explained by another variable.

Counterbalanced design—A research design in which subjects receive two or more treatment conditions balanced in opposite order. The design often is used to reduce the likelihood of learning effects and reduces bias and typically includes randomized assignment to conditions.

Cross-over trial—A cross-over study (trial), is an experimental randomized study in which subjects receive a sequence of different treatments (or exposures) in a sequence that is counterbalanced.

Crude or unadjusted OR— An OR with just on independent (such as cannabis yes or no) and one dependent variable (such as crash yes or no)

Culpability study—Culpability (responsibility) design is a type of observational study in which all drivers have been involved in a crash (usually fatal), and drug tests are taken to assess the presence of drugs. ORs are then calculated to assess the association between being responsible for a crash and testing positive.

Decriminalization— Not treating something as illegal under criminal law.

Deterrence theory—This theory posits that the certainty, swiftness and severity of punishments for offenders will change unwanted behaviours (Ross, 1982). The cornerstone of deterrence is punishment. According to deterrence theory, if undesirable acts are punished then people will be less likely to engage in those behaviours in the future (i.e. specific deterrence) and the larger population will be less likely to engage in behaviours based on fear of being punished (i.e. general deterrence).

Diagnostic test—A test used to determine whether an individual meets a particular condition. In this book the focus is on THC drug tests to determine safety risk.

Discrimination—Unjustified distinctions between human beings based on their group characteristics.

Dispersion—Dispersion (**variability**) is the extent to which a variable is varied. It is statistically measured by standard deviation, variance and coefficient of variation.

Double-blind experimental approach—See *Blinded study*.

Drug Recognition Experts (DRE)—Also called the *Drug Evaluation and Classification Program* (DEC). Developed in the late 1970s by the Los Angeles Police Department, this is a standardized procedure that is used to identify both individuals under the influence of drugs, and the type of drug causing the observable impairment (Beirness et al., 2007).

Driving Under the Influence of Drugs (DRUID) – An archival data set in Europe which documents characteristics of drivers with positive drug tests.

Effect size—This refers to the actual strength of statistical relationships, whether they are correlations, OR or RR. Statistical significance (i.e. $p<.05$) is best thought of as an essential test requirement, and if significant, examines the effect size to assess whether the relationship is meaningful (i.e. has practical implications). In this book, I have defined effect sizes for that I consider weak, moderate or strong different levels of measurement. More details about effect sizes can be found in Chapter 7, Epidemiological guidelines for valid findings, (4) Strength of Association.

Ethanol, also called absolute alcohol—The intoxicating agent found in alcoholic beverages, such as beer, wine and spirits. The amount of ethanol varies considerably among these beverages with average contents of 5% for beers, 12% for wines and 40% for spirits.

Evaluation studies—Studies that assess the success of a program in achieving its goals.

Experiment—An operation or procedure carried out under controlled conditions.

Equilibrium—An equal balance.

External validity—The degree to which the findings of a study can be generalized or translated to groups that did not participate in the study or other conditions. If the results of a study apply to "real-world" conditions, they have good external validity.

False negative—A test result which incorrectly indicates that a particular condition is absent.

False positive—A test result which incorrectly indicates that a particular condition is present.

Fatal Accident Reporting System (FARS) – An archival data set in the U.S. which documents characteristics of fatal crashes.

GC/MS—Gas chromatography and mass spectrometry, a drug testing analytical approach, sometimes referred to as the gold standard.

GC/MS/MS—Gas chromatography coupled with tandem mass spectrometry.

Gold standard for drug tests—These are confirmatory drug tests using chromatography and spectrometry methods to detect a specific compound associated with prior exposure to drugs.

Gold standard for intervention studies— A randomized double-blind study

Gold standard for impairment—An external source of truth regarding the magnitude of deficits known to be associated with increased crash risk.

Harm reduction—A set of practical strategies which are aimed at reducing the negative consequences of drug use without requiring abstinence as a goal. An analogy of this term has been applied to approaches that aim at reducing the likelihood of crashes and injuries to drivers, accepting the fact that people drive, and that driving can be dangerous.

Heterogeneous—A high degree of variability or diverse in character.

Hydroxy-THC (11-OH-THC)—Another major metabolite of THC thought to be psychoactive. Compounds and metabolite concentrations are typically expressed in nano-grams per millilitre (ng/mL). The focus of this book is mainly on detection of THC and these metabolites.

Immunoassay—A screening test that identifies compounds through an antibody test, a test that uses the binding of antibodies to antigens to identify and measure certain substances. It is substantially less valid than confirmatory analyses as it cannot accurately distinguish compounds with similar molecular structures.

Impairment—Refers to a specific threshold at which driving a vehicle due to performance deficits is dangerous for most people. For alcohol, this threshold is .05% and for other drugs, this level has not been determined.

Imputation—The replacement of missing values in a data set based on known characteristics of variables from valid cases.

Independent measures—Each observation on a variable should be independent. This means that multiple observations of the same subject would violate the assumption of independence and should not be used for statistical procedures, such as correlations. One observation should not influence or affect the value of other observations, and multiple observations of the same individuals (i.e. within persons) will tend to be more similar than those of different individuals (i.e. between persons). Violations of this assumption will typically erroneously increase an effect size and sample size, thereby increasing the likelihood of statistical significance.

Indictable offence—A more serious offence under the Criminal Code of Canada.

Internal validity—The degree to which a study is free from bias to allow for strong inferences between suspected cause and effects. Randomized double-blind studies are the gold standard in terms of internal validity. Threats to internal validity represent various explanations of how the results of a study might not be internally valid, based on the designs. These include potential flaws, such as selection (differences found are due to fundamental differences in the group), history

(competing interventions caused the change), experimenter bias, testing effects (both practice effects and Hawthorne effect) and statistical regression.

Intervention study— A research study where exposure, such as cannabis administration, is assigned to subjects in a controlled environment.

Kappa—A statistic often used to assess the degree of agreement between a test and a gold standard, both when both have dichotomous outcomes. Gordis (2014) has provided an interpretation of Kappa values as follows: > .75 excellent agreement, .40 to .75 intermediate to good agreement, < .40 poor agreement.

Laboratory studies—Research studies in controlled environments, which may or may not have randomized conditions.

Limit of Detection—The lowest quantity of a compound that can be distinguished from no compound.

Limit of Quantification— The smallest amount of a compound that can be detected with consistent accuracy.

LC/MS/MS—Liquid chromatography and tandem mass spectrometry, confirmatory methods typically used for detecting specific compounds from oral fluids.

Measurement error—Sometimes referred to as information bias, is an inaccuracy of how a phenomena is measured and interpreted. It can result in the misclassification of subjects.

Mens rea—Criminal intent for a particular behaviour that is a crime.

Metabolite—A compound that is formed by the body's metabolism of a drug.

Meta-analysis— A quantitative analysis of several studies with the same independent and dependent variables. The data from each study is combined into a larger data set to estimate an overall effect.

Multivariate analysis—The statistical assessment of the relationship between two or more independent variables in relation to a dependent variable. Typically, a multivariate analysis would include a main independent variable, thought to be causally related to an outcome, and one or more confounding variables. Age, sex and alcohol consumption are well accepted confounding variables in the study of crashes. The primary purpose of this analysis is to adjust (i.e. remove) the effect of confounding variables in explaining a particular outcome.

Non-significant—Findings from a statistical test where we must conclude that there is no relationship between two or more variables.

Odds Ratio (OR)—The ratio of the odds of getting a disease/health outcome (e.g. crash) if exposed (e.g. cannabis positive) to the odds of getting a disease if unexposed. It is calculated by the formula a*d/c*b (see table below). Although ORs and relative risks are both measures of strength of statistical relationships, and are often treated synonymously by authors, their calculations are different. ORs provide a similar estimate to relative risks when outcomes are infrequent in relation

to exposure, such as in the situation of cannabis-related traffic crashes. Technically, relative risks should be calculated from cohort studies, since incidence data is used; however, many journals will publish relative risks from case-control studies. The terms OR and RR are frequently treated synonymously, though incorrect. ORs also are similar to relative risks when cases and controls are representative of the larger population in terms of exposure and the when the occurrence of a bad outcome is rare.

Cells used for the calculation of ORs

Outcome	Exposed	Unexposed
Disease (e.g. crash, culpable)	a	b
No disease (e.g. no crash, not culpable)	c	d

Observational studies—Studies of human behaviour in the real world.

One-tailed statistical test—A statistical test that only examines one direction of a relationship.

Operational definition—A clear explanation of how to measure something.

Per se law—Per se means "by itself." A per se law for a BAC at or above .08% alcohol means that a person found at this level is considered intoxicated. No further evidence is necessary to demonstrate intoxication.

Performance deficits—Defined more broadly to include any decrements in psychomotor, perceptual or cognitive functioning. Performance deficits do not necessarily mean impairment.

Placebo—A substance of which subjects are not aware that it is inactive.

Plasma—The liquid portion of blood that remains after red blood cells, white blood cells, platelets and other cellular components are removed.

Point-of-collection tests—A fast drug test that gives an indication within 10 minutes of drug exposure.

Positive predictive value—The probability that a person who tests positive truly has a particular condition, such as being impaired.

Prevalence—The proportion of a particular population with a particular condition.

Probability values—The likelihood that the results of a statistical test could be due to chance.

Proportion— a part in relation to the whole.

r and r^2—See Correlation coefficient (r) and Coefficient of determination (r^2).

Randomized selection— A type of sampling approach where each subject chosen for a study is randomly selection.

Randomized assignment design—A study design in which each subject has an equal chance of being assigned to different treatment conditions. Random assignment should not be confused with random selection.

Random breath testing—Stopping drivers and demanding a breath test without reasonable suspicion that the drivers have been drinking.

Ratio—A comparison of two numbers, a fraction or odds.

Receiver Operating Characteristics (ROC)—An analytic approach that compares sensitivity and specificity of a test so that the overall accuracy of the test is maximized.

Recidivism—The likelihood that someone convicted of a crime will re-offend.

Relative risk curve or model—A combination of numerous relative risk point estimates presented in a line chart.

Relative risk or **risk ratio** (**RR**)**—**The ratio of the probability of an event (e.g. crash) in an exposed group (e.g. cannabis positive) to the probability of the event occurring in a non-exposed group (e.g. cannabis negative). It is calculated by the formula: a/(a+b)/c/(c+d) (see table below). Although the formulas for relative risk and OR are different, the terms are sometimes used synonymously. See ORs for more information on the differences between relative risks and ORs.

Cells used for the calculation of relative risk

Outcome	Exposed	Unexposed	Total
Disease (e.g. crash)	a	b	a+b
No disease (e.g. no crash)	c	d	c+d

Reliability—The degree to which an assessment tool produces consistent findings.

Response bias—Bias created in a study in which the respondents are not representative of all the subjects who could have participated.

Selection bias— A type of bias that distorts the magnitude of a statistical relationship and is caused when two groups being compared are dissimilar from each other. This type of bias is often created due to non-respondents, in situations where drug users in the control group are less likely to participate in a study than the cases. It is particularly an issue where consent to participate in the study is required from the control subjects but not the cases. This limitation will also have the effect of creating inflated ORs (higher than reality) because drug users will be under-represented in the control group as they will be less likely to participate.

Selective breath testing—A legal situation where the police require reasonable grounds that a driver has been drinking before administration of a Breathalyzer test.

Sensitivity—Defined as the ability of the test to identify correctly those who have a specific disease (Gordis, 2014; p. 86). In this book, sensitivity is usually referred to as the ability of a test to correctly identify those who are impaired.

Sequential tests—Two tests are used to diagnose a condition where only those who are positive on the first test are subject to a second test that assesses the condition using a different approach. Sequential tests are more appropriate as a diagnostic than screening tests, and increase specificity (i.e. reduce false positives) compared to a single test.

Serum—Serum is the part of blood which is similar in composition with plasma but excludes clotting factors of blood.

Specificity—Ability of a test to identify correctly those who do not have the disease (Gordis, 2014; p. 86). In this book, specificity is usually referred to as the ability of a test to correctly identify those who are **not** impaired.

Spurious— A correlation that is not causal

Standard deviation—A statistical measure used to define the extent of variation or dispersion of a sample. In a normal distribution, about 68% of the observations lie above and below the mean (i.e. average).

Standard deviation of lane position (SDLP)—SDLP is a common measure of weaving when driving, and typically conducted with driving simulators.

Standardized Field Sobriety Tests (SFST)—Three tests used by police to assess behavioural symptoms of alcohol impairment: the one-legged stand, walk and turn and alcohol gaze nystagmus. These tests have been validated against a BAC cut-off of .08%.

Statistical significance—The likelihood that a result or relationship is caused by something other than random chance. The probability value is the likelihood that a given strength of a relationship is due to chance, and for this value to be significant, it should be below 5% or $p<.05$. The likelihood of probability values being significant is based on both the sample size and the variability in the measures. This means that very weak relationships between variables can become significant with a large enough sample.

Stigma—Negative stereotypes or biases against someone based on distinguishing characteristics. In this book, stigma in relation to cannabis users is discussed**.**

Summary offence—These are less serious Criminal Code of Canada offences.

Temperance movements—A social movement against the consumption of alcoholic beverages.

Tetrahydrocannabinol (THC)—The chemical compound responsible for most of cannabis's psychoactive effects.

Titration—The process of adjusting a dosage, typically by smoke inhalation, to obtain the optimal dose of cannabis, which varies considerably from person to person, depending on the level of high or medicinal effect desired.

Transparency— an obligation of researchers to be clear about their methods, analyses and interpretation of their choices that allows others to properly evaluate them.

Two-tailed statistical test—A statistical test that examines two directions of a relationship.

Upward bias— A bias in the methods of a study that leads to a conclusion of a stronger association than reality.

Validity—The degree to which a test measures what it was designed to measure. Validity of the diagnostic test is defined as the ability to distinguish between those who have a disease and those who have not (Gordis, 2014).

Variability—Variability is the extent to which data points in a variable are spread apart.

Whole blood—Blood drawn directly from the body from which no component, such as white and red cells, plasma or platelets, has been removed.

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